

FORM PTO-1390 (REV. 10-2000)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 20430P
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>09/937499</b>
INTERNATIONAL APPLICATION NO. PCT/US00/09587	INTERNATIONAL FILING DATE 10 April 2000	PRIORITY DATE CLAIMED 14 April 1999
TITLE OF INVENTION <b>NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL</b>		
APPLICANT(S) FOR DO/EO/US Konstantin Petrukhin, C. Thomas Caskey, Wen Li and Michael L. Metzker		
<p><b>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</b></p> <ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input type="checkbox"/> This is an express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).</li> <li><input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made and the US was elected by the expiration of the 19th month from the earliest claimed priority date (PCT Article 31).</li> <li><input checked="" type="checkbox"/> A copy of the International Application as filed [35 U.S.C. 371(c)(2)]. a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> <li><input type="checkbox"/> An English language translation of the International Application as filed [35 U.S.C. 371(c)(2)].</li> <li><input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]. a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made.</li> <li><input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].</li> <li><input checked="" type="checkbox"/> An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].</li> <li><input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].</li> </ol>		
<p><b>Items 11 to 16 below concern other document(s) or information included:</b></p> <ol style="list-style-type: none"> <li><input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li><input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li><input type="checkbox"/> A <b>FIRST</b> preliminary amendment. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li><input type="checkbox"/> A substitute specification.</li> <li><input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li><input type="checkbox"/> Other items or information:</li> </ol>		
<div style="text-align: right;"> <b>EXPRESS MAIL CERTIFICATE</b>  <b>DATE OF DEPOSIT</b> <u>Sept. 26 2001</u>  <b>EXPRESS MAIL NO.</b> <u>EF180606849US</u>  <b>I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS</b>  <b>BEING DEPOSITED WITH THE UNITED STATES POSTAL</b>  <b>SERVICE AS EXPRESS MAIL "POST OFFICE TO</b>  <b>ADDRESSEE" BEFORE 5 PM ON THE ABOVE DATE IN</b>  <b>AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER</b>  <b>FOR PATENTS, WASHINGTON, D.C. 20231</b>  <b>MAILED BY</b> <u>A. J. G. (Agent)</u>  <b>DATE</b> <u>Sept. 26 2001</u> </div>		

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>09/937499</b>	INTERNATIONAL APPLICATION NO. PCT/US00/20430	ATTORNEY'S DOCKET NUMBER 20430P		
17. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE [37 CFR 1.492(a)(1)-(5)]:</b>		CALCULATIONS PTO USE ONLY		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee [37 CFR 1.445(a)(2)] paid to USPTO and International Search Report not prepared by the EPO or JPO..... \$1,000.00				
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..... \$860.00				
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee [37 CFR 1.445(a)(2)] paid to USPTO..... \$710.00				
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... \$690.00				
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)..... \$100.00				
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		\$100.00		
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date [37 CFR 1.492(e)].		\$0.00		
Claims	Number Filed	Number Extra	Rate	
Total Claims	21 - 20 =	1	X \$18.00	\$18.00
Independent Claims	12 - 3 =	9	X \$80.00	\$720.00
Multiple dependent claim(s) (if applicable)		0	+ \$270.00	\$0.00
<b>TOTAL OF ABOVE CALCULATIONS =</b>		\$838.00		
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				
<b>SUBTOTAL =</b>		\$838.00		
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date [37 CFR 1.492(f)].		+ \$0.00		
<b>TOTAL NATIONAL FEE =</b>		\$838.00		
Fee for recording the enclosed assignment [37 CFR 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property.		+ \$0.00		
<b>TOTAL FEES ENCLOSED =</b>		\$838.00		
		Amount to be refunded		
		charged		
<p>a. <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>13-2755</u> in the amount of <u>\$838.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to the Deposit Account No. <u>13-2755</u>. A duplicate copy of this sheet is enclosed.</p>				
<p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive [37 CFR 1.137(a) or (b)] must be filed and granted to restore the application to pending status.</b></p>				
SEND ALL CORRESPONDENCE TO:				
<p>MERCK &amp; CO., INC. Patent Department, RY60-30 P.O. Box 2000 126 East Lincoln Avenue Rahway, New Jersey 07065-0970</p>				
<p>DATE: <u>9/26/01</u></p>				
<p>PHONE #: <u>(732) 594-6734</u></p>				
<p> SIGNATURE Joseph A. Coppola NAME 38,413 REGISTRATION NUMBER</p>				

09/937499

## TITLE OF THE INVENTION

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

## CROSS-REFERENCE TO RELATED APPLICATIONS

5 Not applicable.

## STATEMENT REGARDING FEDERALLY-SPONSORED R&amp;D

Not applicable.

## 10 REFERENCE TO MICROFICHE APPENDIX

Not applicable.

## FIELD OF THE INVENTION

15 The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel.

## BACKGROUND OF THE INVENTION

20 Voltage-gated potassium channels form transmembrane pores that open in response to changes in cell membrane potential and selectively allow potassium ions to pass through the membrane. Many voltage-gated potassium channels have been identified. They are distinguishable by tissue-specific patterns of expression as well as by electrophysiological and pharmacological properties.

25 Voltage-gated potassium channels have been shown to be involved in maintaining cell membrane potentials and controlling the repolarization of action potentials in many cells, *e.g.*, neurons, muscle cells, and pancreatic  $\beta$  cells. They are important targets for drug discovery in connection with a variety of diseases.

30 Functional voltage-gated potassium channels are believed to be tetramers of four alpha subunits, each of which contains six transmembrane spanning segments. The alpha subunits making up a tetramer may be the same (in the case of homotetramers) or may be different (in the case of heterotetramers). The membrane-spanning alpha subunits making up the tetramers may sometimes be associated with additional, beta subunits, which may alter the behavior of the tetramers.

For reviews of voltage-gated potassium channels see Robertson, 1997, Trends Pharmacol. Sci. 18:474-483; Jan & Jan, 1997, J. Physiol. 505:267-282; Catterall, 1995, Ann. Rev. Biochem. 64:493-531.

Macular dystrophy is a term applied to a heterogeneous group of 5 diseases that collectively are the cause of severe visual loss in a large number of people. A common characteristic of macular dystrophy is a progressive loss of central vision resulting from the degeneration of the pigmented epithelium underlying the retinal macula. In many forms of macular dystrophy, the end stage of the disease results in legal blindness. More than 20 types of macular dystrophy are known: e.g., 10 age-related macular dystrophy, Stargardt's and Stargardt-like macular dystrophy, cone-rod dystrophies, atypical vitelliform macular dystrophy (VMD1), Usher Syndrome Type 1B, autosomal dominant neovascular inflammatory vitreoretinopathy, familial exudative vitreoretinopathy, and Best's macular dystrophy. For a review of the macular dystrophies, see Sullivan & Daiger, 1996, Mol. Med. Today 2:380-386.

15 Cone-rod dystrophies involve an initial loss of cone photoreceptors followed by the degeneration of rod photoreceptors. This loss of photoreceptors can lead to blindness. Cone-rod dystrophies appear to be a heterogeneous group of inherited disorders for which multiple chromosomal locations have been implicated (Evans et al., 1994, Nature Genet. 6:210-213; Kelsell et al., 1997, Hum. Mol. Genet. 20 6:597-600). In particular, Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279 found a candidate gene (CORD7) located at chromosome 6q in a four-generation British family affected with cone-rod dystrophy. A marker in 6q, D6S280, showed a high LOD score of 3.31 (at genetic distance = 0).

25 Stargardt-like macular dystrophy is an inherited, dominant retinal disease. Affected individuals have normal vision in early childhood but show impaired central vision either in late childhood or early adulthood. The first observable characteristics of the disease are flecks seen in the macula. This is followed by central atrophy, resulting in visual acuity decreasing to 20/200 or worse (Stone et al., Arch. Ophthalmol. 112:765-772 [Stone]). Stone mapped a gene 30 responsible for Stargardt-like macular dystrophy to chromosome 6q. The marker D6S280 was observed by Stone to have the high LOD score of 5.5 (at genetic distance = 0).

Cone-rod dystrophy and Stargardt-like macular dystrophy appear different from a clinical perspective. For example, Stargardt-like macular dystrophy

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generally begins in childhood and involves white/yellow flecks in the retina while cone-rod dystrophy is an adult-onset disorder in which no flecks are present. Despite such clinical differences, both diseases may be caused by mutations in the same gene. It is not uncommon for different mutations in a single gene to give rise to clinically 5 different disorders. For example, depending upon the particular mutation, mutations in the peripherin/RDS gene can give rise to either butterfly-shaped pigment dystrophy of the fovea, retinitis pigmentosa, pattern dystrophy, flavus maculatus, macular dystrophy, or central areolar choroidal dystrophy (Nichols et al., 1993, *Nature Genet.* 3:202-207; Weleber et al., 1993, *Arch. Ophthalmol.* 111:1531-1542; Wells et al., 10 *Nature Genet.* 3:213-218; Reig et al., 1995, *Ophthalmic. Genet.* 16:39-44).

While studies of macular dystrophies such as cone-rod dystrophy or Stargardt-like macular dystrophy are valuable in themselves, such studies are also valuable in that they are expected to shed light on age-related macular degeneration (AMD). AMD is the leading cause of severe visual loss in older individuals. Genetic 15 factors apparently play a role in AMD (Hyman et al., 1983, *Am. J. Epidemiol.* 118:213-227; Gass, 1973, *Arch. Ophthalmol.* 90:206-217). It is believed likely that mild allelic variations of such earlier-onset diseases as cone-rod dystrophy and Stargardt-like macular dystrophy are responsible for some cases of AMD. Thus, 20 understanding and developing treatments for these earlier-onset diseases should prove valuable with respect to AMD as well.

Salla disease is a recessive condition characterized by early-onset psychomotor retardation and ataxia that involves defects in the lysosomal transport of sialic acid. Leppänen et al., 1996, *Genomics* 37:62-67 (Leppänen) located the gene for Salla disease in the immediate vicinity of the marker D6S280. Leppänen screened 25 a PAC library with the marker D6S280 and obtained three positive clones, among which were PAC 141B1 and PAC 224H23, strongly suggesting that the gene for Salla disease is present on these PACs.

## SUMMARY OF THE INVENTION

30 The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel, KCNQ5, located in a chromosomal region that contains a gene associated with Stargardt-like macular dystrophy, cone-rod macular dystrophy, and Salla disease.

The present invention includes genomic KCNQ5 DNA as well as cDNA that encodes the KCNQ5 protein. The human genomic KCNQ5 DNA is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:1. The human cDNA encoding KCNQ5 protein is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:2. Also provided is KCNQ5 protein encoded by the novel DNA sequences. The human KCNQ5 protein is substantially free from other proteins and has the amino acid sequence shown in SEQ.ID.NO.:3. Methods of expressing KCNQ5 protein in recombinant systems are provided as well as methods of identifying activators and inhibitors of KCNQ5 protein function. Also provided are diagnostic methods that detect carriers of mutant KCNQ5 genes.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-AO shows the genomic DNA sequence of human KCNQ5 (SEQ.ID.NO.:1). Underlined nucleotides in capitals represent exons. The start ATG codon in exon 1 and the stop TAA codon in exon 14 are shown in bold italics. The D6D280 genetic marker and a phosphoglycerate pseudogene are underlined in bold. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, and 13 and 14 are unknown. These gaps are represented as runs of ten bold ns for the sake of convenience.

Figure 2A-E shows the nucleotide sequence (SEQ.ID.NO.:2) and encoded amino acid sequence (SEQ.ID.NO.:3) of human KCNQ5 cDNA. The ATG start codon is at position 138; the TAA stop codon is at position 2,676.

Figure 3A shows the results of a Northern blot of KCNQ5 mRNA expression in various human tissues. Figure 3B shows the results of RT-PCR analysis of KCNQ5 mRNA expression in various human tissues.

Figure 4A shows a sequence alignment of human KCNQ5 protein (SEQ.ID.NO.:3) with human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:5). Figure 4B-C shows a multiple sequence alignment between human KCNQ5 protein (SEQ.ID.NO.:3), human KCNQ1 protein (SEQ.ID.NO.:43), human KCNQ2 protein (SEQ.ID.NO.:6), human KCNQ3 protein (SEQ.ID.NO.:7), and human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:8).

## DETAILED DESCRIPTION OF THE INVENTION

For the purposes of this invention:

“Substantially free from other proteins” means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other proteins.

5 Thus, a KCNQ5 protein preparation that is substantially free from other proteins will contain, as a percent of its total protein, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 proteins. Whether a given KCNQ5 protein preparation is substantially free from other proteins can be determined by such conventional techniques of assessing protein purity as, *e.g.*, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) combined with appropriate detection methods, *e.g.*, silver staining or immunoblotting.

10 “Substantially free from other nucleic acids” means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other nucleic acids. Thus, a KCNQ5 DNA preparation that is substantially free from other nucleic acids will contain, as a percent of its total nucleic acid, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 nucleic acids. Whether a given KCNQ5 DNA preparation is substantially free from other nucleic acids can be determined by such conventional techniques of assessing nucleic acid purity as, *e.g.*, agarose gel electrophoresis combined with appropriate staining methods, *e.g.*, ethidium bromide staining, or by sequencing.

15 A “conservative amino acid substitution” refers to the replacement of one amino acid residue by another, chemically similar, amino acid residue. Examples of such conservative substitutions are: substitution of one hydrophobic residue (isoleucine, leucine, valine, or methionine) for another; substitution of one polar residue for another polar residue of the same charge (*e.g.*, arginine for lysine; glutamic acid for aspartic acid); substitution of one aromatic amino acid (tryptophan, tyrosine, or phenylalanine) for another.

20 30 A polypeptide has “substantially the same biological activity as KCNQ5” if that polypeptide conducts a voltage-gated potassium current when expressed in appropriate cell types and has an amino acid sequence that is at least about 50% identical to SEQ.ID.NO.:3 when measured by such standard programs as BLAST or FASTA.

The present invention relates to the identification and cloning of KCNQ5, a gene encoding a novel voltage-gated potassium channel. The human KCNQ5 gene is located on chromosome 6q14, in a chromosomal region that contains genes that have been linked with the occurrence of at least three diseases: Stargardt-like macular dystrophy, cone-rod dystrophy, and Salla disease.

The human KCNQ5 gene is present on PAC clones from chromosomal region 6q14. PAC141B1 was sequenced and KCNQ5 was found based on homology between the genomic sequences of KCNQ5 present in PAC 141B1 and the sequences of known potassium channel genes. PAC 141B1 is available from Research Genetics, Inc., Huntsville, AL, as an individual clone from the RPCI4,5,6 Library (catalog number CTLLC). Using PCR primers derived from the KCNQ5 sequence, a cDNA sequence representing the coding region as well as a large portion of the 3'-UTR of KCNQ5 was isolated from a human fetal brain cDNA library. Comparison of this cDNA clone with the genomic sequences present in PAC141B1, as well as KCNQ5 sequences found in PAC224H23, showed that exons 3-11 and portions of flanking intronic regions are present in PAC141B1. Exon 2 and flanking intronic regions were found in PAC224H23, while the rest of the KCNQ5 gene (exons 1, 12-14, and flanking intronic regions) was recovered from total human genomic DNA by using cDNA primers and a GenomeWalker kit from Clontech, Palo Alto, CA.

PAC141B1 and PAC224H23 are located in the region of the Salla disease gene (Leppänen et al., 1996, Genomics 37:62-67). PAC141B1 contains the polymorphic genetic marker D6S280 that is located in intron 3 of the KCNQ5 gene between exons 3 and 4 (Figure 1). D6S280 is the marker that detects the maximum LOD score of 5.5 (at genetic distance = 0) in families with Stargardt-like macular dystrophy (Stone et al., Arch. Ophthalmol. 112:765-772). D6S280 also detects a LOD score of 3.31 (at genetic distance = 0) in families with cone-rod dystrophy (Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279). These LOD scores indicate that D6S280 is very closely linked to, and probably is within, the gene for Stargardt-like macular dystrophy and cone-rod dystrophy. In view of these findings, it is likely that KCNQ5 is involved in Salla disease, Stargardt-like macular dystrophy, and cone-rod dystrophy.

That KCNQ5 should be involved with these three diseases is consistent with its expression pattern (see Figure 3A-B) which shows that KCNQ5 is expressed predominately in the retina and brain, in addition to being expressed in the

skeletal muscle. Stargardt-like macular dystrophy and cone-rod dystrophy are inherited retinal diseases while Salla disease is a disorder that is characterized by early onset psychomotor retardation and ataxia.

5 Bioinformatic analysis revealed a striking homology of the KCNQ5 protein to a group of voltage gated potassium channels (KCNQ1, KCNQ2, KCNQ3, and KCNQ4; see Figure 4A-B). All of the typical amino acid motifs of these potassium channels are preserved in KCNQ5. A Kyte-Doolittle algorithm analysis predicts a transmembrane organization for KCNQ5 that is typical for this group of potassium channels. Mutations in members of this family of potassium channels have been shown to result in inherited disease (KCNQ2 and KCNQ3, epilepsy [Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690]; KCNQ4, a form of nonsyndromic dominant deafness [Kubisch et al., 1999, Cell 96:437-446], KCNQ1, congenital long QT syndrome which causes cardiac arrhythmias and sudden death [Splawski et al., 1997, N. Engl. J. Med. 336:1562-1567]).

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The present invention provides DNA encoding KCNQ5 that is substantially free from other nucleic acids. The present invention also provides recombinant DNA molecules encoding KCNQ5. The present invention provides DNA molecules substantially free from other nucleic acids comprising the nucleotide sequence shown in Figure 1 as SEQ.ID.NO.:1. Analysis of SEQ.ID.NO.:1 revealed that this genomic sequence defines a gene having 14 exons. These exons collectively have an open reading frame that encodes a protein of 846 amino acids.

20 The present invention includes cDNA encoding KCNQ5 protein. Such a cDNA is shown in Figure 2 as SEQ.ID.NO.:2. The present invention therefore includes DNA comprising the nucleotide sequence SEQ.ID.NO.:2. The DNA can be isolated or substantially free of other DNA sequences.

25

The present invention includes DNA molecules substantially free from other nucleic acids comprising the coding region of SEQ.ID.NO.:2. Accordingly, the present invention includes DNA molecules substantially free from other nucleic acids having a sequence comprising positions 138-2,675 of SEQ.ID.NO.:2. Also included are recombinant DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2 and isolated DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2.

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The novel DNA sequences of the present invention encoding KCNQ5, in whole or in part, can be linked with other DNA sequences, *i.e.*, DNA sequences to which KCNQ5 is not naturally linked, to form “recombinant DNA molecules” encoding KCNQ5. Such other sequences can include DNA sequences that control transcription or translation such as, *e.g.*, translation initiation sequences, promoters for RNA polymerase II, transcription or translation termination sequences, enhancer sequences, sequences that control replication in microorganisms, sequences that confer antibiotic resistance, or sequences that encode a polypeptide “tag” such as, *e.g.*, a polyhistidine tract or the myc epitope. The novel DNA sequences of the present invention can be inserted into vectors such as plasmids, cosmids, viral vectors, P1 artificial chromosomes, or yeast artificial chromosomes.

Included in the present invention are DNA sequences that hybridize to at least one of SEQ.ID.NO:1 or SEQ.ID.NO:2 under stringent conditions. By way of example, and not limitation, a procedure using conditions of high stringency is as follows: Prehybridization of filters containing DNA is carried out for 2 hr. to overnight at 65°C in buffer composed of 6X SSC, 5X Denhardt's solution, and 100 µg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hrs at 65°C in prehybridization mixture containing 100 µg/ml denatured salmon sperm DNA and 5-20 X 10<sup>6</sup> cpm of <sup>32</sup>P-labeled probe. Washing of filters is done at 37°C for 1 hr in a solution containing 2X SSC, 0.1% SDS. This is followed by a wash in 0.1X SSC, 0.1% SDS at 50°C for 45 min. before autoradiography.

Other procedures using conditions of high stringency would include either a hybridization carried out in 5XSSC, 5X Denhardt's solution, 50% formamide at 42°C for 12 to 48 hours or a washing step carried out in 0.2X SSPE, 0.2% SDS at 65°C for 30 to 60 minutes.

Reagents mentioned in the foregoing procedures for carrying out high stringency hybridization are well known in the art. Details of the composition of these reagents can be found in, *e.g.*, Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press. In addition to the foregoing, other conditions of high stringency which may be used are well known in the art.

The degeneracy of the genetic code is such that, for all but two amino acids, more than a single codon encodes a particular amino acid. This allows for the construction of synthetic DNA that encodes the KCNQ5 protein where the nucleotide

sequence of the synthetic DNA differs significantly from the nucleotide sequences of SEQ.ID.NO:2, but still encodes the same KCNQ5 protein as SEQ.ID.NO:2. Such synthetic DNAs are intended to be within the scope of the present invention.

Mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 are intended to be 5 within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 which give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

Another aspect of the present invention includes host cells that have 10 been engineered to contain and/or express DNA sequences encoding KCNQ5 protein. Such recombinant host cells can be cultured under suitable conditions to produce KCNQ5 protein. An expression vector containing DNA encoding KCNQ5 protein can be used for expression of KCNQ5 protein in a recombinant host cell.

Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, 15 bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of human, bovine, porcine, monkey and rodent origin, amphibian cells such as *Xenopus* oocytes, and insect cells including but not limited to *Drosophila* and silkworm derived cell lines. Cells and cell lines which are suitable for recombinant expression of KCNQ5 protein and which are widely available, 20 include but are not limited to, L cells L-M(TK-) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), 25 ARPE-19 human retinal pigment epithelium (ATCC CRL-2302), *Xenopus* melanophores, and *Xenopus* oocytes.

A variety of mammalian expression vectors can be used to express recombinant KCNQ5 in mammalian cells. Commercially available mammalian expression vectors which are suitable include, but are not limited to, pMC1neo 30 (Stratagene), pSG5 (Stratagene), pcDNAI and pcDNAIamp, pcDNA3, pcDNA3.1, pCR3.1 (Invitrogen), EBO-pSV2-neo (ATCC 37593), pBPV-1(8-2) (ATCC 37110), pdBPV-MMTneo(342-12) (ATCC 37224), pRSVgpt (ATCC 37199), pRSVneo (ATCC 37198), and pSV2-dhfr (ATCC 37146). Another suitable vector is the PT7TS oocyte expression vector. Following expression in recombinant cells, KCNQ5 can

be purified by conventional techniques to a level that is substantially free from other proteins.

Certain voltage-gated potassium channel subunits have been found to require the expression of other voltage-gated potassium channel subunits as 5 "chaperones" in order to be properly expressed at high levels and inserted in membranes. For example, co-expression of KCNQ3 appears to enhance the expression of KCNQ2 in *Xenopus* oocytes (Wang et al., 1998, *Science* 282:1890-1893). Also, some voltage-gated potassium channel Kv1 $\alpha$  subunits require other related alpha subunits or Kv $\beta$ 2 subunits (Shi et al., 1995, *Neuron* 16:843-852).

10 Accordingly, the recombinant expression of the KCNQ5 protein may under certain circumstances benefit from the co-expression of other voltage-gated potassium channel proteins and such co-expression is intended to be within the scope of the present invention.

15 The present invention includes KCNQ5 protein substantially free from other proteins. The amino acid sequence of the full-length KCNQ5 protein is shown in Figure 2 as SEQ.ID.NO.:3. Thus, the present invention includes KCNQ5 protein substantially free from other proteins having the amino acid sequence SEQ.ID.NO.:3. The present invention also includes isolated KCNQ5 protein having the amino acid sequence SEQ.ID.NO.:3.

20 Mutated forms of KCNQ5 proteins are intended to be within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:3 that give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

25 As with many proteins, it is possible to modify many of the amino acids of KCNQ5 and still retain substantially the same biological activity as the original protein. Thus, the present invention includes modified KCNQ5 proteins which have amino acid deletions, additions, or substitutions but that still retain substantially the same biological activity as KCNQ5. It is generally accepted that single amino acid substitutions do not usually alter the biological activity of a protein 30 (see, e.g., Molecular Biology of the Gene, Watson et al., 1987, Fourth Ed., The Benjamin/Cummings Publishing Co., Inc., page 226; and Cunningham & Wells, 1989, *Science* 244:1081-1085). Accordingly, the present invention includes polypeptides where one amino acid substitution has been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as

KCNQ5. The present invention also includes polypeptides where two or more amino acid substitutions have been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as KCNQ5. In particular, the present invention includes embodiments where the above-described substitutions are 5 conservative substitutions. In particular, the present invention includes embodiments where the above-described substitutions do not occur in positions where the amino acid present in KCNQ5 is also present in the corresponding position of any one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4 (see Figure 4A-B).

10 The KCNQ5 proteins of the present invention may contain post-translational modifications, *e.g.*, covalently linked carbohydrate, phosphorylation, myristylation, *etc.*.

15 The present invention also includes chimeric KCNQ5 proteins. Chimeric KCNQ5 proteins consist of a contiguous polypeptide sequence of at least a portion of KCNQ5 protein fused to a polypeptide sequence of a non-KCNQ5 protein.

20 The present invention also includes isolated forms of KCNQ5 proteins and KCNQ5 DNA. Use of the term "isolated" indicates that KCNQ5 protein or KCNQ5 DNA has been removed from its normal cellular environment. Thus, an isolated KCNQ5 protein may be in a cell-free solution or placed in a different cellular environment from that in which it occurs naturally. The term isolated does not imply that an isolated KCNQ5 protein is the only protein present, but instead means that an isolated KCNQ5 protein is at least 95% free of non-amino acid material (*e.g.*, nucleic acids, lipids, carbohydrates) naturally associated with the KCNQ5 protein. Thus, a KCNQ5 protein that is expressed in bacteria or even in eukaryotic cells which do not naturally (*i.e.*, without human intervention) express it through recombinant means is 25 an "isolated KCNQ5 protein."

30 It is known that other members of the family of potassium channels to which KCNQ5 belongs can interact to form heteromeric structures resulting in functional potassium channels. For example, KCNQ2 and KCNQ3 can assemble to form a heteromeric functional potassium channel (Wang et al., 1998, *Science* 282:1890-1893). Accordingly, it is believed likely that KCNQ5 will also be able to form heteromeric structures with other proteins where such heteromeric structures constitute functional potassium channels. Thus, the present invention includes such heteromers comprising KCNQ5. Preferred heteromers are those in which KCNQ5 forms heteromers with at least one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4.

A cDNA fragment encoding full-length KCNQ5 can be isolated from a human retinal or brain cDNA library by using the polymerase chain reaction (PCR) employing suitable primer pairs. Such primer pairs can be selected based upon the cDNA sequence for KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2. Suitable primer 5 pairs would be, *e.g.*:

5'-GGGGGCCCGGATGAGCC-3' (SEQ.ID.NO.:9) and  
5'-GAAGAACTTATTCAGTTGA-3' (SEQ.ID.NO.:10)

The above primers are meant to be illustrative only; one skilled in the art would readily be able to design other suitable primers based upon SEQ.ID.NO.:2. 10 Such primers could be produced by methods of oligonucleotide synthesis that are well known in the art.

PCR reactions can be carried out with a variety of thermostable enzymes including but not limited to AmpliTaq, AmpliTaq Gold, or Vent polymerase. For AmpliTaq, reactions can be carried out in 10 mM Tris-Cl, pH 8.3, 2.0 mM 15 MgCl<sub>2</sub>, 200 μM for each dNTP, 50 mM KCl, 0.2 μM for each primer, 10 ng of DNA template, 0.05 units/μl of AmpliTaq. The reactions are heated at 95°C for 3 minutes and then cycled 35 times using the cycling parameters of 95°C, 20 seconds, 62°C, 20 seconds, 72°C, 3 minutes. In addition to these conditions, a variety of suitable PCR protocols can be found in PCR Primer. A Laboratory Manual, edited by C.W. 20 Dieffenbach and G.S. Dveksler, 1995, Cold Spring Harbor Laboratory Press; or PCR Protocols: A Guide to Methods and Applications, Michael *et al.*, eds., 1990, Academic Press .

A suitable cDNA library from which a clone encoding KCNQ5 can be isolated would be Human Retina 5'-stretch cDNA library in lambda gt10 or lambda 25 gt11 vectors (catalog numbers HL1143a and HL1132b, Clontech, Palo Alto, CA) or human fetal brain 5-stretch plus cDNA library (catalog number HL5024t, Clontech, Palo Alto, CA). The primary clones of such a library can be subdivided into pools with each pool containing approximately 20,000 clones and each pool can be amplified separately.

30 By this method, a cDNA fragment encoding an open reading frame of 846 amino acids (SEQ.ID.NO.:3) can be obtained. This cDNA fragment can be cloned into a suitable cloning vector or expression vector. For example, the fragment can be cloned into the mammalian expression vector pcDNA3.1 (Invitrogen, San Diego, CA). KCNQ5 protein can then be produced by transferring an expression

vector encoding KCNQ5 or portions thereof into a suitable host cell and growing the host cell under appropriate conditions. KCNQ5 protein can then be isolated by methods well known in the art.

As an alternative to the above-described PCR method, a cDNA clone 5 encoding KCNQ5 can be isolated from a cDNA library using as a probe oligonucleotides specific for KCNQ5 and methods well known in the art for screening cDNA libraries with oligonucleotide probes. Such methods are described in, *e.g.*, Sambrook *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York; Glover, D.M. (ed.), 1985, *DNA 10 Cloning: A Practical Approach*, MRL Press, Ltd., Oxford, U.K., Vol. I, II. Oligonucleotides that are specific for KCNQ5 and that can be used to screen cDNA libraries can be readily designed based upon the cDNA sequence of KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2 and can be synthesized by methods well-known in the art.

Genomic clones containing the KCNQ5 gene can be obtained from 15 commercially available human PAC or BAC libraries available from Research Genetics, Huntsville, AL. PAC clones containing the KCNQ5 gene (*e.g.*, PAC141B1, PAC224H23) are commercially available from Research Genetics, Huntsville, AL (catalog number for individual PAC clones is RPCI.C). Alternatively, one may prepare genomic libraries, especially in P1 artificial chromosome vectors, from which 20 genomic clones containing the KCNQ5 can be isolated, using probes based upon the KCNQ5 sequences disclosed herein. Methods of preparing such libraries are known in the art (Ioannou *et al.*, 1994, *Nature Genet.* 6:84-89).

The novel DNA sequences of the present invention can be used in 25 various diagnostic methods relating to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. The present invention provides diagnostic methods for determining whether a patient carries a mutation in the KCNQ5 gene that predisposes that patient toward the development of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In broad terms, such methods comprise determining the DNA sequence 30 of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not suffer from Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the

patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Such methods of diagnosis may be carried out in a variety of ways.

5 For example, one embodiment comprises:

(a) providing PCR primers from a region of the KCNQ5 gene;

(b) performing PCR on a DNA sample from the patient to produce a PCR fragment from the patient;

(c) performing PCR on a control DNA sample comprising a

10 nucleotide sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2 to produce a control PCR fragment;

(d) determining the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment;

(e) comparing the nucleotide sequence of the PCR fragment from 15 the patient to the nucleotide sequence of the control PCR fragment;

where a difference between the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment indicates that the patient has a mutation in the KCNQ5 gene and thus is likely to have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related 20 macular degeneration.

In a particular embodiment, the PCR primers are from a region of the KCNQ5 gene where it is suspected that a patient harbors a mutation. In a particular embodiment, the PCR primers are from the coding region of the KCNQ5 gene, *i.e.*, from the coding region of SEQ.ID.NO:1 or SEQ.ID.NO:2. In a particular 25 embodiment, the PCR primers amplify a region that includes the marker D6S280.

In a particular embodiment, the DNA sample from the patient is cDNA that has been prepared from an RNA sample from the patient. In another embodiment, the DNA sample from the patient is genomic DNA. In a particular embodiment, the control DNA sample is DNA from a person who does not have 30 Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are determined by DNA sequencing.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are compared by direct comparison after DNA sequencing. In another embodiment, step (d) is omitted and the comparison in step (e) is made by a process that includes hybridizing the PCR fragment from the patient and the control PCR fragment and then using an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly. Such an endonuclease is, *e.g.*, S1. In this embodiment, the conversion of the PCR fragment from the patient to smaller fragments after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene. In such embodiments, it may be advantageous to label (radioactively, enzymatically, immunologically, *etc.*) the PCR fragment from the patient or the control PCR fragment.

10 The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

- 15 (a) obtaining an RNA sample from the patient;
- (b) performing reverse transcription-PCR (RT-PCR) on the RNA sample using primers that span a region of the coding sequence of the KCNQ5 gene to produce a PCR fragment from the patient where the PCR fragment from the patient has a defined length, the length being dependent upon the identity of the primers that were used in the RT-PCR;
- 20 (c) hybridizing the PCR fragment to DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or to portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels, to form a hybrid;
- 25 (d) treating the hybrid produced in step (c) with an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly;
- (e) determining whether the endonuclease cleaved the hybrid by determining the length of the PCR fragment from the patient after endonuclease treatment where a reduction in the length of the PCR fragment from the patient after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene.

30 In a variation of the above-described method, instead of determining the length of the PCR fragment from the patient after endonuclease treatment, the

length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels is determined after endonuclease treatment. In such a variation, a 5 reduction in the length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels indicates that the patient carries a mutation in the KCNQ5 gene.

10 The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

- (a) making cDNA from an RNA sample from the patient;
- (b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;
- (c) performing PCR on the cDNA to produce a PCR fragment from the patient;
- (d) determining the nucleotide sequence of the PCR fragment from the patient;
- (e) comparing the nucleotide sequence of the PCR fragment from 15 the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2; where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

20 The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

- (a) preparing genomic DNA from the patient;
- (b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;
- (c) performing PCR on the genomic DNA to produce a PCR fragment from the patient;
- (d) determining the nucleotide sequence of the PCR fragment from the patient;
- (e) comparing the nucleotide sequence of the PCR fragment from 25 the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention also provides oligonucleotide probes, based 5 upon the sequences of SEQ.ID.NO:1 or SEQ.ID.NO:2, that can be used in diagnostic methods related to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In particular, the present invention includes DNA oligonucleotides comprising at least about 10, 15, or 18 contiguous nucleotides of a sequence selected from the group consisting of: SEQ.ID.NO:1 and 10 SEQ.ID.:NO.2 where the oligonucleotide probe comprises no stretch of contiguous nucleotides longer than 5 of a sequence selected from the group consisting of: SEQ.ID.NO:1 and SEQ.ID.:NO.2 other than the said at least about 10, 15, or 18 contiguous nucleotides. The oligonucleotides can be substantially free from other nucleic acids. Also provided by the present invention are corresponding RNA 15 oligonucleotides. The DNA or RNA oligonucleotide probes can be packaged in kits.

In addition to the diagnostic utilities described above, the present invention makes possible the recombinant expression of the KCNQ5 protein in various cell types. Such recombinant expression makes possible the study of this protein so that its biochemical activity and its role in Stargardt-like macular 20 dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration can be elucidated.

The present invention also makes possible the development of assays which measure the biological activity of the KCNQ5 protein. Such assays using recombinantly expressed KCNQ5 protein are especially of interest. Assays for 25 KCNQ5 protein activity can be used to screen libraries of compounds or other sources of compounds to identify compounds that are activators or inhibitors of the activity of KCNQ5 protein. Such identified compounds can serve as "leads" for the development of pharmaceuticals that can be used to treat patients having Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular 30 degeneration. In versions of the above-described assays, mutant KCNQ5 proteins are used and inhibitors or activators of the activity of the mutant KCNQ5 proteins are identified.

Preferred cell lines for recombinant expression of KCNQ5 are those which do not express endogenous potassium channels (e.g., CV-1, NIH-3T3). Such

cell lines can be loaded with  $^{86}\text{Rb}$ , an ion which can pass through potassium channels. The  $^{86}\text{Rb}$ -loaded cells can be exposed to collections of substances (e.g., combinatorial libraries, natural products) and those substances that are able to alter  $^{86}\text{Rb}$  efflux identified. Such substances are likely to be activators or inhibitors of 5 KCNQ5.

The present invention includes a method of identifying activators or inhibitors of KCNQ5 comprising:

(a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;

10 (b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

15 where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

In particular embodiments, the biological activity is the production of a voltage-gated potassium current, or efflux of  $^{86}\text{Rb}$ .

20 In particular embodiments, a vector encoding KCNQ5 is transferred into *Xenopus* oocytes in order to cause the expression of KCNQ5 protein in the oocytes. Alternatively, RNA encoding KCNQ5 protein can be prepared *in vitro* and injected into the oocytes, also resulting in the expression of KCNQ5 protein in the oocytes. Following expression of KCNQ5 in the oocytes, membrane currents are measured after the transmembrane voltage is changed in steps. A change in 25 membrane current is observed when the KCNQ5 channels opens, allowing potassium ion flow. Similar oocytes studies were reported for KCNQ2 and KCNQ3 potassium channels in Wang et al., 1998, *Science* 282:1890-1893.

30 Inhibitors of KCNQ5 can be identified by exposing the oocytes expressing KCNQ5 to collections of substances and determining whether the substances can block or diminish the membrane currents observed in the absence of the substance.

Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

(a) expressing KCNQ5 protein in *Xenopus* oocytes;

(b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;

(c) measuring membrane potassium currents following step (b); where if the potassium membrane currents measured in step (c) are

5 greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

The present invention also includes assays for the identification of activators and inhibitors of KCNQ5 that are based upon FRET between a first and a second fluorescent dye where the first dye is bound to one side of the plasma membrane of a cell expressing KCNQ5 and the second dye is free to shuttle from one face of the membrane to the other face in response to changes in membrane potential. In certain embodiments, the first dye is impenetrable to the plasma membrane of the cells and is bound predominately to the extracellular surface of the plasma membrane. The second dye is trapped within the plasma membrane but is free to diffuse within

10 the membrane. At normal (*i.e.*, negative) resting potentials of the membrane, the second dye is bound predominately to the inner surface of the extracellular face of the plasma membrane, thus placing the second dye in close proximity to the first dye. This close proximity allows for the generation of a large amount of FRET between the two dyes. Following membrane depolarization, the second dye moves from the

15 extracellular face of the membrane to the intracellular face, thus increasing the distance between the dyes. This increased distance results in a decrease in FRET, with a corresponding increase in fluorescent emission derived from the first dye and a corresponding decrease in the fluorescent emission from the second dye. See figure 1 of González & Tsien, 1997, Chemistry & Biology 4:269-277. See also González &

20 Tsien, 1995, Biophys. J. 69:1272-1280 and U.S. Patent No. 5,661,035.

25

In certain embodiments, the first dye is a fluorescent lectin or a fluorescent phospholipid that acts as the fluorescent donor. Examples of such a first dye are: a coumarin-labeled phosphatidylethanolamine (*e.g.*, N-(6-chloro-7-hydroxy-2-oxo-2H-1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidyl-30 ethanolamine) or N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); a fluorescently-labeled lectin (*e.g.*, fluorescein-labeled wheat germ agglutinin). In certain embodiments, the second dye is an oxonol that acts as the fluorescent acceptor. Examples of such a second dye are: bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols (*e.g.*, bis(1,3-dihexyl-2-

thiobarbiturate)trimethineoxonol) or pentamethineoxonol analogues (*e.g.*, bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; or bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol). See González & Tsien, 1997, Chemistry & Biology 4:269-277 for methods of synthesizing various dyes suitable for use in the present invention. In certain embodiments, the assay may comprise a natural carotenoid, *e.g.*, astaxanthin, in order to reduce photodynamic damage due to singlet oxygen.

The above described assays can be utilized to discover activators and inhibitors of KCNQ5. Such assays will generally utilize cells that express KCNQ5, *e.g.*, by transfection with expression vectors encoding KCNQ5. In assays for inhibitors, such cells will generally have a resting membrane potential that is roughly equal to the threshold for activation of the KCNQ5 channel. This is because most untransfected cells will have membrane potentials that are depolarized relative to the threshold potential of KCNQ5 channels. Therefore, when KCNQ5 is expressed in these cells, the KCNQ5 channels open. This lets K<sup>+</sup> out of the cells, which tends to hyperpolarize the membrane potential. This closes some of the KCNQ5 channels, leading to relative depolarization. In this way, a steady state develops around the threshold for activation of the KCNQ5 channel. Inhibitors of KCNQ5 will, therefore, disturb this steady state and depolarize the cell. In assays for activators, KCNQ5 will be transfected into a cell line that also expresses a counteracting, depolarizing current. The membrane potential in these cells will therefore be set by contributions of both the KCNQ5 channel and the endogenous depolarizing current, resulting in a more depolarized resting potential. Ideally, the endogenous current will play the major role in the absence of a KCNQ5 activator. Activators of KCNQ5 will open this channel and increase the contribution of KCNQ5 to the membrane potential relative to the other current and the potential will, therefore, hyperpolarize in response to an activator of KCNQ5. Changes in membrane potential (depolarizations and hyperpolarizations) that are caused by activators and inhibitors of KCNQ5 can be monitored by the assays using FRET described above.

Accordingly, the present invention provides a method of identifying activators of KCNQ5 comprising:

- (a) providing test cells comprising:
  - (1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

The present invention also provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

5 wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

10 where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

15 In a variation of the assay described above, instead of the transfected cell's membrane potential being allowed to reach steady state on its own, the membrane potential is artificially set at a potential in which the KCNQ5 channel is open. This can be done, *e.g.*, by variation of the external K<sup>+</sup> concentration in a known manner (*e.g.*, increased concentrations of external K<sup>+</sup>). If such cells, having open KCNQ5 channels, are exposed to inhibitors of KCNQ5, the KCNQ5 channels will close, and the cells' membrane potentials will be depolarized. This depolarization can be observed as a decrease in FRET.

20 Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

25 (2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

30 (b) adjusting the membrane potential of the cells such that the ion channel formed by KCNQ5 is open;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells;

(d) repeating step (b) and step (c) while the cells are exposed to a substance that is suspected of being an inhibitor of KCNQ5;

where if the amount of FRET exhibited by the cells that are exposed to the substance is less than the amount of FRET exhibited by the cells that have not been exposed to the substance, then the substance is an inhibitor of KCNQ5.

5 In particular embodiments of the above-described methods, the expression vectors are transfected into the test cells.

In particular embodiments of the above-described methods, KCNQ5 has an amino acid sequence of SEQ.ID.NO.:3.

10 In particular embodiments of the above-described methods, the first fluorescent dye is selected from the group consisting of: a fluorescent lectin; a fluorescent phospholipid; a coumarin-labeled phosphatidylethanolamine; N-(6-chloro-7-hydroxy-2-oxo-2H-1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidylethanolamine; N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); and fluorescein-labeled wheat germ agglutinin.

15 In particular embodiments of the above-described methods, the second fluorescent dye is selected from the group consisting of: an oxonol that acts as the fluorescent acceptor; bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)trimethineoxonol; bis(1,3-dialkyl-2-thiobarbiturate)quatramethineoxonols; bis(1,3-dialkyl-2-thiobarbiturate)pentamethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol); and bis(1,3-dialkyl-2-thiobarbiturate)hexamethineoxonols.

20 In a particular embodiment of the above-described methods, the cells are eukaryotic cells. In another embodiment, the cells are mammalian cells. In other embodiments, the cells are L cells L-M(TK<sup>-</sup>) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), *Xenopus*Xenopus oocytes.

25 In particular embodiments of the above-described methods, the control cells do not comprise item (a)(1) but do comprise items (a)(2) and (a)(3).

5 In assays to identify activators or inhibitors of KCNQ5, it may be advantageous to co-express another potassium channel, *e.g.*, KCNQ1, KCNQ2, KCNQ3, or KCNQ4, together with KCNQ5, or with an accessory subunit, such as the IsK protein or one of its homologues, in order to form a functional heteromeric potassium channel.

10 While the above-described methods are explicitly directed to testing whether “a” substance is an activator or inhibitor of KCNQ5, it will be clear to one skilled in the art that such methods can be adapted to test collections of substances, *e.g.*, combinatorial libraries, to determine whether any members of such collections are activators or inhibitors of KCNQ5. Accordingly, the use of collections of substances, or individual members of such collections, as the substance in the above-described methods is within the scope of the present invention.

15 The present invention includes pharmaceutical compositions comprising activators or inhibitors of KCNQ5 protein that have been identified by the herein-described methods. The activators or inhibitors are generally combined with pharmaceutically acceptable carriers to form pharmaceutical compositions. Examples of such carriers and methods of formulation of pharmaceutical compositions containing activators or inhibitors and carriers can be found in Remington’s 20 Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain a therapeutically effective amount of the activators or inhibitors.

25 Therapeutic or prophylactic compositions are administered to an individual in amounts sufficient to treat or prevent conditions where KCNQ5 activity is abnormal. The effective amount can vary according to a variety of factors such as the individual’s condition, weight, gender, and age. Other factors include the mode of administration. The appropriate amount can be determined by a skilled physician.

Compositions can be used alone at appropriate dosages. Alternatively, co-administration or sequential administration of other agents can be desirable.

30 The compositions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for administration. For example, the compositions can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they can also be administered in intravenous (both bolus and infusion),

intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

Advantageously, compositions can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, compositions can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dosage regimen utilizing the compositions is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal, hepatic and cardiovascular function of the patient; and the particular composition thereof employed. A physician of ordinary skill can readily determine and prescribe the effective amount of the composition required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of composition within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the composition's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a composition.

The present invention includes a method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration and other forms of macular degeneration, deafness, epilepsy, and different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

When screening compounds in order to identify potential pharmaceuticals that specifically interact with a target ion channel, it is necessary to ensure that the compounds identified are as specific as possible for the target ion channel. To do this, it is necessary to screen the compounds against as wide an array as possible of ion channels that are similar to the target ion channel. Thus, in order to find compounds that are potential pharmaceuticals that interact with ion channel A, it

is not enough to ensure that the compounds interact with ion channel A (the “plus target”) and produce the desired pharmacological effect through ion channel A. It is also necessary to determine that the compounds do not interact with ion channels B, C, D, *etc.* (the “minus targets”). In general, as part of a screening program, it is 5 important to have as many minus targets as possible (see Hodgson, 1992, Bio/Technology 10:973-980, at 980). KCNQ5 protein, DNA encoding KCNQ5 protein, and recombinant cells that have been engineered to express KCNQ5 protein have utility in that they can be used as “minus targets” in screens designed to identify 10 compounds that specifically interact with other ion channels. For example, Wang et al., 1998, Science 282:1890-1893 have shown that KCNQ2 and KCNQ3 form a heteromeric potassium ion channel known as the “M-channel.” The M-channel is an important target for drug discovery since mutations in KCNQ2 and KCNQ3 are responsible for causing epilepsy (Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690). A 15 screening program designed to identify activators or inhibitors of the M-channel would benefit greatly by the use of KCNQ5 as a minus target.

The present invention also includes antibodies to the KCNQ5 protein. Such antibodies may be polyclonal antibodies or monoclonal antibodies. The 20 antibodies of the present invention are raised against the entire KCNQ5 protein or against suitable antigenic fragments of the protein that are coupled to suitable carriers, *e.g.*, serum albumin or keyhole limpet hemocyanin, by methods well known in the art. Methods of identifying suitable antigenic fragments of a protein are known in the art. See, *e.g.*, Hopp & Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828; and Jameson & Wolf, 1988, CABIOS (Computer Applications in the Biosciences) 4:181-186.

For the production of polyclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected on a periodic basis into an appropriate non-human host animal such as, *e.g.*, rabbits, sheep, goats, rats, mice. The animals are bled periodically and sera obtained are tested for the presence of 30 antibodies to the injected antigen. The injections can be intramuscular, intraperitoneal, subcutaneous, and the like, and can be accompanied with adjuvant.

For the production of monoclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected into an appropriate non-human host animal as above for the production of polyclonal antibodies. In the case

of monoclonal antibodies, the animal is generally a mouse. The animal's spleen cells are then immortalized, often by fusion with a myeloma cell, as described in Kohler & Milstein, 1975, *Nature* 256:495-497. For a fuller description of the production of monoclonal antibodies, see Antibodies: A Laboratory Manual, Harlow & Lane, eds., 5 Cold Spring Harbor Laboratory Press, 1988.

Gene therapy may be used to introduce KCNQ5 polypeptides into the cells of target organs, *e.g.*, the pigmented epithelium of the retina or other parts of the retina. Nucleotides encoding KCNQ5 polypeptides can be ligated into viral vectors which mediate transfer of the nucleotides by infection of recipient cells. Suitable 10 viral vectors include retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, lentivirus, and polio virus based vectors. Alternatively, nucleotides encoding KCNQ5 polypeptides can be transferred into cells for gene therapy by non-viral techniques including receptor-mediated targeted transfer using ligand-nucleotide conjugates, lipofection, membrane fusion, or direct microinjection. These procedures 15 and variations thereof are suitable for *ex vivo* as well as *in vivo* gene therapy. Gene therapy with KCNQ5 polypeptides will be particularly useful for the treatment of diseases where it is beneficial to elevate KCNQ5 activity.

The present invention includes processes for cloning orthologues of human KCNQ5 from non-human species. In general, such processes include 20 preparing a PCR primer or a hybridization probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that can be used to amplify a fragment containing the non-human KCNQ5 (in the case of PCR) from a suitable DNA preparation or to select a cDNA or genomic clone containing the non-human KCNQ5 from a suitable library. A preferred embodiment of this process is a process for cloning the KCNQ5 gene from 25 mouse.

By providing DNA encoding mouse KCNQ5, the present invention allows for the generation of an animal model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. Such animal models can be generated by making transgenic "knockout" or "knockin" mice 30 containing altered KCNQ5 genes. Knockout mice can be generated in which portions of the mouse KCNQ5 gene have been deleted. Knockin mice can be generated in which mutations that have been shown to lead to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration when present in the human KCNQ5 gene are introduced into the mouse gene. Such knockout and

knockin mice will be valuable tools in the study of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration and will provide important model systems in which to test potential pharmaceuticals or treatments for Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

5 Accordingly, the present invention includes a method of producing a mouse model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration comprising:

- (a) designing PCR primers or an oligonucleotide probe based upon 10 SEQ.ID.NO.:1 or SEQ.ID.NO.:2 for use in cloning the mouse KCNQ5 gene;
- (b) using the PCR primers or the oligonucleotide probe to clone at least a portion of the mouse KCNQ5 gene, the portion being large enough to use in making a transgenic mouse;
- (c) producing a transgenic mouse having at least one copy of the 15 mouse KCNQ5 gene altered from its native state.

Methods of producing knockout and knockin mice are well known in the art. One method involves the use of gene-targeted ES cells in the generation of gene-targeted transgenic knockout mice and is described in, *e.g.*, Thomas et al., 1987, Cell 51:503-512, and is reviewed elsewhere (Frohman et al., 1989, Cell 56:145-147; 20 Capecchi, 1989, Trends in Genet. 5:70-76; Baribault et al., 1989, Mol. Biol. Med. 6:481-492).

Techniques are available to inactivate or alter any genetic region to virtually any mutation desired by using targeted homologous recombination to insert specific changes into chromosomal genes. Generally, use is made of a "targeting 25 vector," *i.e.*, a plasmid containing part of the genetic region it is desired to mutate. By virtue of the homology between this part of the genetic region on the plasmid and the corresponding genetic region on the chromosome, homologous recombination can be used to insert the plasmid into the genetic region, thus disrupting the genetic region. Usually, the targeting vector contains a selectable marker gene as well.

30 In comparison with homologous extrachromosomal recombination, which occurs at frequencies approaching 100%, homologous plasmid-chromosome recombination was originally reported to only be detected at frequencies between  $10^{-6}$  and  $10^{-3}$  (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395; Smithies et al., 1985, Nature 317: 230-234; Thomas et al., 1986, Cell 44:419-428).

Nonhomologous plasmid-chromosome interactions are more frequent, occurring at levels 10<sup>5</sup>-fold (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395) to 10<sup>2</sup>-fold (Thomas et al., 1986, Cell 44:419-428) greater than comparable homologous insertion.

5 To overcome this low proportion of targeted recombination in murine ES cells, various strategies have been developed to detect or select rare homologous recombinants. One approach for detecting homologous alteration events uses the polymerase chain reaction (PCR) to screen pools of transformant cells for homologous insertion, followed by screening individual clones (Kim et al., 1988, 10 Nucleic Acids Res. 16:8887-8903; Kim et al., 1991, Gene 103:227-233). Alternatively, a positive genetic selection approach has been developed in which a marker gene is constructed which will only be active if homologous insertion occurs, allowing these recombinants to be selected directly (Sedivy et al., 1989, Proc. Natl. Acad. Sci. USA 86:227-231). One of the most powerful approaches developed for 15 selecting homologous recombinants is the positive-negative selection (PNS) method developed for genes for which no direct selection of the alteration exists (Mansour et al., 1988, Nature 336:348-352; Capecchi, 1989, Science 244:1288-1292; Capecchi, 1989, Trends in Genet. 5:70-76). The PNS method is more efficient for targeting genes which are not expressed at high levels because the marker gene has its own 20 promoter. Nonhomologous recombinants are selected against by using the Herpes Simplex virus thymidine kinase (HSV-TK) gene and selecting against its nonhomologous insertion with herpes drugs such as gancyclovir (GANC) or FIAU (1-(2-deoxy 2-fluoro-B-D-arabinofuranosyl)-5-iodouracil). By this counter-selection, the percentage of homologous recombinants in the surviving transformants can be 25 increased.

Other methods of producing transgenic mice involve microinjecting the male pronuclei of fertilized eggs. Such methods are well known in the art.

30 The following non-limiting examples are presented to better illustrate the invention.

## EXAMPLE 1

Identification of the human KCNQ5 gene and cDNA cloningConstruction of Libraries for Shotgun Sequencing from PAC Clones

Bacterial strains containing the KCNQ5 PACs (P1 Artificial Chromosomes) were received from Research Genetics (Huntsville, AL). Cells were streaked on Luria-Bertani (LB) agar plates supplemented with the appropriate antibiotic. A single colony was used to prepare a 5-ml starter culture and then 1-L overnight culture in LB medium. The cells were pelleted by centrifugation and PAC DNA was purified by equilibrium centrifugation in cesium chloride-ethidium bromide gradient (Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press). Purified PAC DNA was brought to 50 mM Tris pH 8.0, 15 mM MgCl<sub>2</sub>, and 25% glycerol in a volume of 2 ml and placed in a AERO-MIST nebulizer (CIS-US, Bedford, MA). The nebulizer was attached to a nitrogen gas source and the DNA was randomly sheared at 10 psi for 30 sec. The sheared DNA was ethanol precipitated and resuspended in TE (10 mM Tris, 1 mM EDTA). The ends were made blunt by treatment with Mung Bean Nuclease (Promega, Madison, WI) at 30°C for 30 min, followed by phenol/chloroform extraction, and treatment with T4 DNA polymerase (GIBCO/BRL, Gaithersburg, MD) in multicore buffer (Promega, Madison, WI) in the presence of 40 uM dNTPs at 16°C. To facilitate subcloning of the DNA fragments, BstX I adapters (Invitrogen, Carlsbad, CA) were ligated to the fragments at 14°C overnight with T4 DNA ligase (Promega, Madison, WI). Adapters and DNA fragments less than 500 bp were removed by column chromatography using a cDNA sizing column (GIBCO/BRL, Gaithersburg, MD) according to the instructions provided by the manufacturer. Fractions containing DNA greater than 1 kb were pooled and concentrated by ethanol precipitation. The DNA fragments containing BstX I adapters were ligated into the BstX I sites of pSHOT II which was constructed by subcloning the BstX I sites from pcDNA II (Invitrogen, Carlsbad, CA) into the BssH II sites of pBlueScript (Stratagene, La Jolla, CA). pSHOT II was prepared by digestion with BstX I restriction endonuclease and purified by agarose gel electrophoresis. The gel purified vector DNA was extracted from the agarose by following the Prep-A-Gene (BioRad, Richmond, CA) protocol. To reduce ligation of

the vector to itself, the digested vector was treated with calf intestinal phosphatase (GIBCO/BRL, Gaithersburg, MD. Ligation reactions of the DNA fragments with the cloning vector were transformed into ultra-competent XL-2 Blue cells (Stratagene, La Jolla, CA), and plated on LB agar plates supplemented with 100 µg/ml ampicillin.

5 Individual colonies were picked into a 96 well plate containing 100 µl/well of LB broth supplemented with ampicillin and grown overnight at 37°C. Approximately 25 µl of 80% sterile glycerol was added to each well and the cultures stored at -80°C.

#### Preparation of plasmid DNA

10 Glycerol stocks were used to inoculate 5 ml of LB broth supplemented with 100 µg/ml ampicillin either manually or by using a Tecan Genesis RSP 150 robot (Tecan AG, Hombrechtikon, Switzerland) programmed to inoculate 96 tubes containing 5 ml broth from the 96 wells. The cultures were grown overnight at 37°C with shaking to provide aeration. Bacterial cells were pelleted by centrifugation , the 15 supernatant decanted, and the cell pellet stored at -20°C. Plasmid DNA was prepared with a QIAGEN Bio Robot 9600 (QIAGEN, Chatsworth, CA) according to the Qiawell Ultra protocol. To test the frequency and size of inserts, plasmid DNA was digested with the restriction endonuclease Pvu II. The size of the restriction 20 endonuclease products was examined by agarose gel electrophoresis with the average insert size being 1 to 2 kb.

#### DNA Sequence Analysis of Shotgun clones

25 DNA sequence analysis was performed using the ABI PRISM™ dye terminator cycle sequencing ready reaction kit with AmpliTaq DNA polymerase, FS (Perkin Elmer, Norwalk, CT). DNA sequence analysis was performed with M13 forward and reverse primers. Following amplification in a Perkin-Elmer 9600, the extension products were purified and analyzed on an ABI PRISM 377 automated sequencer (Perkin Elmer, Norwalk, CT). Approximately 4 sequencing reactions were performed per kb of DNA to be examined (384 sequencing reactions per each of nine 30 PACs).

#### Assembly of DNA sequences

Phred/Phrap was used for DNA sequences assembly. This program was developed by Dr. Phil Green and licensed from the University of Washington

(Seattle, WA). Phred/Phrap consists of the following programs: Phred for base-calling, Phrap for sequence assembly, Crossmatch for sequence comparisons, Consed and Phrapview for visualization of data, Repeatmasker for screening repetitive sequences. Vector and *E. coli* DNA sequences were identified by Crossmatch and removed from the DNA sequence assembly process. DNA sequence assembly was on a SUN Enterprise 4000 server running a Solaris 2.51 operating system (Sun Microsystems Inc., Mountain View, CA) using default Phrap parameters. The sequence assemblies were further analyzed using Consed and Phrapview.

10 Genomic sequence of the KCNQ5 gene and its exon/intron organization

Genomic DNA sequence from PAC 141B1 was compared with GenBank database entries using the BLASTN and BLASTX algorithms of the AceDB package. This comparison originally revealed a total of 5 exons (exons 3(D), 4 (A), 5(B), 6(E), and 7(C) delineated in Figure1), based on their homology to the known 15 potassium channel genes KCNQ1, KCNQ2, KCNQ3, and KCNQ4. Full-length cDNA was rescued from the pools of the human fetal brain cDNA library using the RCCA technique described in Example 2. Comparison of the cDNA sequence and genomic sequence of PAC141B1 revealed a total of 8 exons (exons 3-10 delineated in Figure1). Genomic regions corresponding to exons 1,2, and 11-14 were not present in 20 PAC141B1.

In order to identify the genomic region corresponding to exon 2 and its right flanking intron, oligonucleotide KCN-2L2 (TTTCTCCTTGTCTTGTTGCTTG; SEQ.ID.NO.:11) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2L1 (CCTCAAGTTGCCTTGATCCTG; SEQ.ID.NO.:13) in combination with the nested adaptor primer AP2 (ACTCACTATAAGGGCTCGAGCGGC; 30 SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 2 and its left flanking intron, oligonucleotide KCN-2R1 (CAGGATCAAGAGGCAATTGAGG; SEQ.ID.NO.:15) from the KCNQ5 cDNA in combination with the adaptor primer AP1

(CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2R2 (CCAATTGTGTGCTCAGGGATGGTAGA; SEQ.ID.NO.:16) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its right flanking intron, oligonucleotide KCN-11L1 (GACACAGCCCTGGCACT; SEQ.ID.NO.:17) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-11L2 (GATGATGTATATGATGAAAAAGGATG; SEQ.ID.NO.:18) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its left flanking intron, oligonucleotide KCN-11R1 (CTGATAGCTCGAATGACAGTTT; SEQ.ID.NO.:19) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCACTG; SEQ.ID.NO.:20) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its right flanking intron, oligonucleotide KCN-12L1 (AGA ATT ATG AAA TTT CAT GTT GCA; SEQ.ID.NO.:21) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12L2 (AAA CGG AAG TTT AAG GAA ACA TT; SEQ.ID.NO.:22) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its left flanking intron, oligonucleotide KCN-12R1 (ACG TGT TTG TTG GCT TTT AAT TC; SEQ.ID.NO.:23) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAACATCGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12R2 ( TAC ACA ACA TGT CCA GAT GAC; SEQ.ID.NO.:24) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its right flanking intron, oligonucleotide KCN-13L1 (TGATCAAATTCTGGAAAAGGG; SEQ.ID.NO.:25) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAACATCGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13L2 (TCACATCAGATAAGAAGAGCCGA; SEQ.ID.NO.:26) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its left flanking intron, oligonucleotide KCN-13R1 (GTTTTCAACCTTGACCACCC; SEQ.ID.NO.:27) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAACATCGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13R2 (AGCATACTGAGATCGTCTGTGGT; SEQ.ID.NO.:28) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 14 and its left flanking intron, oligonucleotide KCN-2543R(AATTCCAAAAGTGTCTGTCTGT; SEQ.ID.NO.:29) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAACATCGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-

amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2512R (GGACCCACCTCTTCATCAGTTA; SEQ.ID.NO.:30) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

Products obtained from these PCR amplifications were analyzed using ABI 377 sequencers according to standard protocols. Comparison of the full-length KCNQ5 cDNA sequence with the sequences of PAC141B1 and sequences obtained in PCR reactions with DNA from the GenomeWalker kit revealed all 14 exons of the KCNQ5 gene. Exact sequence of exon/intron boundaries within the KCNQ5 gene were determined for exons 2-14. The splice signals in all introns conform to published consensus sequences.

## EXAMPLE 2

### 15 Cloning of KCNQ5 cDNA

The DNA sequence of the cDNA fragment that matches exons 3(D), 4 (A), 5(B), 6(E), and 7(C) of the KCNQ5 was deduced from the genomic sequence of PAC 141B1. Subsequent sequencing of PCR fragments obtained in RCCA reactions confirmed the presence of this fragment in the cDNA library from human fetal brain. This original cDNA fragment corresponds to the cDNA region with coordinates 368-1,004 in Figure 2.

A PCR based technique termed Reduced Complexity cDNA Analysis (RCCA) was used to extend this original cDNA fragment. RCCA is similar to procedures reported by Munroe et al., 1995, Proc. Natl. Acad. Sci. USA 92: 2209-2213 and Wilfinger et al., 1997, BioTechniques 22:481-486 and relies upon a PCR template that is a pool of approximately 20,000 cDNA clones; this reduces the complexity of the template and increases the probability of obtaining longer PCR extensions.

96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 483 bp PCR product using primers KCN-DL (GGAAGACTGAGGTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32). Eight wells were found to

contain the correct 483 bp fragment by PCR analysis. 5' and 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTACACTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primers KCN-DL and KCN-ER because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primers KCN-EL (CTTCTTGCACCTCCTGCC; SEQ.ID.NO.37) and KCN-DR1 (AACACAGAAGGGCTTCGAG; SEQ.ID.NO.38). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30  $\mu$ l of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2\_16\_99" that corresponds to the cDNA region with coordinates 278-1,456 in Figure 2. A second round of the RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 2\_16\_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 117 bp PCR product using primers KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) and KCN-11R1 (CTGATAGCTCGAATGACAGTTT; SEQ.ID.NO.19) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 2\_16\_99". A number of wells were found to contain the correct 117 bp fragment by PCR analysis. 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTACACTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer

KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.20). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30  $\mu$ l of water. The products were analyzed on ABI 377 sequencers according to

5 standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2\_26\_99" that corresponds to the cDNA region with coordinates 278-2,527 in Figure 2. A third round of RCCA analysis was performed to obtain the clones extending to the 5' end of the cDNA contig termed "KCN consensus 2\_26\_99". 96 wells of a

10 human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 214 bp PCR product using primers KCN-2L2

(TTTCTCCTTGTCTTGGTTGCTTG; SEQ.ID.NO.11) and KCN-DR1

(AACACAGAAGGGCTTCGAG; SEQ.ID.NO.38) that were derived from the 5' sequence of the cDNA contig termed "KCN consensus 2\_26\_99". A number of

15 wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGGCTTACACTTATGCTTCC; SEQ.ID.NO.34) were both used in

20 combination with gene specific primer KCN-DR1

(AACACAGAAGGGCTTCGAG; SEQ.ID.NO.38) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R

(CCAGGGTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F

25 (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-DR2 (CAGTCTCCTTGCATCCTC; SEQ.ID.NO.39). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30  $\mu$ l of water. The products were analyzed on ABI 377 sequencers according to standard

30 protocols.

PCR fragments were assembled into a contig termed "KCN consensus 3\_3\_99" that corresponds to the cDNA region with coordinates 1-2,527 in Figure 2. A fourth round of RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 3\_3\_99". 96 wells of a human

fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 145 bp PCR product using primers KCN-2106L (GCAGCCCCAACAACTTTACA; SEQ.ID.NO.40) and KCN-2250R (CATTTCCTGGAGGCAACA; SEQ.ID.NO.41) that were derived from the 3' sequence of the cDNA contig termed 5 "KCN consensus 3\_3\_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers , PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F 10 (CCCAGGCTTACACTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-2106L (GCAGCCCCAACAACTTTACA; SEQ.ID.NO.40) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R 15 (CCAGGGTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-2165L (GCCAGAAACTCTGCACCCCTA; SEQ.ID.NO.42). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 20 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols; PCR fragments were assembled into a contig termed "KCN consensus 3\_15\_99" that corresponds to the cDNA sequence depicted in Figure 2.

### EXAMPLE 3

25 Analysis of expression of KCNQ5

*RT-PCR:* RT-PCR experiments were performed on "quick-clone" human cDNA samples available from Clontech, Palo Alto, CA. cDNA samples from heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, and retina were amplified with primers KCN-DL (GGAAGACTGAGGTTGCTCG; SEQ.ID.NO.31) 30 and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) in the following PCR conditions:

1. 94°C 10 min
2. 94°C 30 sec
3. 72°C 2 min (decrease this temperature by 1.1°C per cycle)
4. 72°C 2 min
5. 5. Go to step 2 21 more times
6. 94°C 30 sec
7. 55°C 2 min
8. 72°C 2 min
9. Go to step 6 19 more times
10. 10. 72°C 7 min
11. 4°C

The KCNQ5 gene was found to be predominantly expressed in human retina and brain (Figure 3B).

15

*Northern blot analysis:* Northern blots containing poly(A+)-RNA from human heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas were purchased from Clontech, Palo Alto, CA. Primers KCN-DL (GGAAGACTGAGGTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) were used to amplify a PCR product of 483 bp from a quick-clone human retina cDNA available from Clontech, Palo Alto, CA. This fragment was purified on an agarose gel, the DNA extracted and used as a probe for Northern blot hybridization.

15 The probe was labeled by random priming with the Amersham Rediprime kit (Arlington Heights, IL) in the presence of 50-100 µCi of 3000 Ci/mmol [alpha 32P]dCTP (Dupont/NEN, Boston, MA). Unincorporated nucleotides were removed with a ProbeQuant G-50 spin column (Pharmacia/Biotech, Piscataway, NJ). The radiolabeled probe at a concentration of greater than  $1 \times 10^6$  cpm/ml in rapid hybridization buffer (Clontech, Palo Alto, CA) was incubated overnight at 65°C. The blots were washed by two 15 min incubations in 2X SSC, 0.1% SDS (prepared from 20X SSC and 20 % SDS stock solutions, Fisher, Pittsburgh, PA) at room temperature, followed by two 15 min incubations in 1X SSC, 0.1% SDS at room temperature, and two 30 min incubations in 0.1X SSC, 0.1% SDS

at 60°C. Autoradiography of the blots was done to visualize the bands that specifically hybridized to the radiolabeled probe.

The probe hybridized to an mRNA transcript that is predominately expressed in brain and retina (Figure 3A).

5

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the 10 scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

## WHAT IS CLAIMED IS:

1. An isolated DNA comprising nucleotides encoding a KCNQ5 protein.

5

2. The DNA of claim 1 comprising nucleotides encoding a polypeptide having the amino acid sequence SEQ.ID.NO.:3.

10 3. The DNA of claim 1 comprising a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1, SEQ.ID.NO.:2, and positions 138-2,675 of SEQ.ID.NO.:2.

15 4. An isolated DNA that hybridizes under stringent conditions to a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

20

5. An expression vector comprising the DNA of claim 1.

6. A recombinant host cell comprising the DNA of claim 1.

25

7. An isolated KCNQ5 protein.

8. The KCNQ5 protein of claim 7 having the amino acid sequence SEQ.ID.NO.:3.

30

9. The KCNQ5 protein of claim 8 containing a single amino acid substitution.

10. The KCNQ5 protein of claim 8 containing two or more amino acid substitutions where the amino acid substitutions do not occur in a position where the amino acid substituted in KCNQ5 is also present in the corresponding position of any one of KCNQ2, KCNQ3, or KCNQ4.

11. An antibody that binds specifically to a KCNQ5 protein where the KCNQ5 protein has the amino acid sequence SEQ.ID.NO.:3.

12. A method of diagnosing whether a patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration that comprises determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

15 13. A method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) providing a DNA sample from the patient;  
(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;  
(c) performing PCR on the DNA sample to produce a PCR fragment from the patient;  
(d) determining the nucleotide sequence of the PCR fragment from the patient;  
(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2; where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

30 14. The method of claim 13 where the DNA sample is genomic DNA.

15. The method of claim 13 where the DNA sample is cDNA.

16. A DNA or RNA oligonucleotide probe comprising at least 18 contiguous nucleotides of at least one of a sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

5

17. A method for determining whether a substance is an activator or an inhibitor of a KCNQ5 protein or a mutant KCNQ5 protein comprising:

(a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;

10

(b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

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18. A method of identifying inhibitors of KCNQ5 comprising:

(a) expressing KCNQ5 protein in *Xenopus* oocytes;

(b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;

(c) measuring membrane potassium currents following step (b);

where if the potassium membrane currents measured in step (c) are greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

25

19. A method of identifying activators of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of

30

KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

5 (b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

10 (d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

15 where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

20. A method of identifying inhibitors of KCNQ5 comprising:

20 (a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

25 (3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

30 (c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

5 where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

10 21. A method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration, other forms of macular degeneration, deafness, epilepsy, different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

15

### FIGURE 1A

### KCN6q gene: DNA sequence

1. Underlined nucleotides in capitals represent exons.
2. Initiating ATG codon in exon 1 and terminating TAA codon in exon 14 are shown in bold italics
3. D6D280 genetic marker and phosphoglycerate mutase pseudogene are bold underlined
4. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, 13 and 14 are unknown; these gaps are presented as runs of ten bold n as a convenience only

1 CTGGAGTGTAG GCGCGGGAAAG ATGCCCTGGTC CTTGCCCTCGC GGACTTGGCA  
51 GCCGCGTCCT GCGGGCTGTG CCACTGAACT GCTGAGGACT GCGGCGGTGG  
101 CCTGAGGGAG AGCCGCCGGG GCAAGCAGGG GGCCCGGATG AGCCTGCTGG  
151 GGAAGCCGCT CTCTTACACG AGTAGCCAGA GCTGCCGGCG CAACGTCAAG  
201 TACCGGGCGGG TGCAGAACTA CCTGCTACAAAC GTGCTGGAGA GACCCCCGCGG  
251 CTGGGCCTTC ATCTACCACG CTTCGTnnn nnnnnnnnn tttttctatt  
301 cttattatta atatatgtac ttattattaa taatataaag gaatagcaaa  
351 tgagaatcca tgagcaatat cagaccatga aatgagcca gtggctgagt  
401 aacaaccaat taggacactt gatagtttag caaagtgc aaacaggaga  
451 cagactcggc tccttgaac gaagagtgac tgcagtgtgg attccccaga  
501 taggagagca agaacatact ttctgggcct ctctcaggat cgttggtttg  
551 gaagaagtt gtatggaaa ttcacaaaact cttagatgt aacatttaaa  
601 tgcagcatgc cacacacaca aaccacaaa cacaaccc ttttcatcaa  
651 taaaattgca gaggagcccc atttgcacag tatatcacat tgatattttaa  
701 tatccaaaat ggctagttcc ttccagagtt ttatagagtt aatgtgtctg  
751 aatttaatgg gcctgggtct ttattcattt gaagcaagaa attaagtctg  
801 tgataataag gtaaaggttt tatccatgtt ctctttttgt tgttttacag  
851 TTTTCTCCTT GTCTTGGTT GCTTGTATTT GTCAGTGT TCTACCACATCC  
901 CTGAGCACAC AAAATTGGCC TCAAGTTGCC TCTTGATCCT Ggtaaagtgaa  
951 acatgaacaa gaacgtacat gaatgttgc taagaactgc ctataacatt  
1001 tatactatgc atcttatact acaaaaaaat cctatctaa aaagagttac  
1051 tgagaaatat aaaaatgtca aaagattactg aaacatttc ccaccaattt  
1101 aacatgtagt caatccttag aaatataatag aaatgttc gattgctatt  
1151 acacagcaat atcttgcgtt gtagatataat cataaaataga aggcaatatt  
1201 agaaaagcgt tttaagtatg tttatctatg ctaataaaca aattatataaa  
1251 gaagaatcag tatctatgc gcctctcatt atattgtgaa agactataga  
1301 gtagagagca ttttccaaata actgtatattt ggcagtagct aaatataatt  
1351 ggccaaagaac tatgaacata tggcacctca taagaaaata gaaggctct  
1401 tcatgtctt ttcaaccaac agactgcatt atgagtttgc ctgctaattgc  
1451 agttacacctgg tgataaaattc tgcagtttgc tctgtttcca ttatgtgtc  
1501 aatccctcaac cacacagaat tgctcaattt actttnnnnn nnnnnacag  
1551 gtcaggaggt cgagaccatc ctgcctaaca cggtgaaacc ccgcctctac  
1601 taaaaataca aaaaatttagc tggcgtagc tactcaggag gctgaggcag  
1651 gagaatggcg tgaacacctgg aggcggagct tgcagttagc cgagattgc  
1701 tcactgcact ccagcgacag agccagactc cgtctcaaaa aaaaaaaaaa  
1751 aaaaaaaaaaa gagtataact gatttatggc atgagttgtc ttgaatgatt  
1801 ttgtatggatg acttggaaaca attagagata taaataaata gcacagaatc  
1851 atgcacagat tcatgaagaa tacactgtga agattcaca ggttaataac  
1901 atggaaattt ttaaaaataaa agagactgc tatattatgt tttctttgt  
1951 gatctatgtt ttcaaagcag cagaaaaactt taaattttcc ttaattttga  
2001 aagtgtgatt aatggaaat tgttacaatg ccattgtatt atatactttg  
2051 aggatagttt acttctttat gttttattaga aattgcactg agagctaata  
2101 tgcagtttct attgggtgtt atatgttctg ttaacagggc ctctgtcag  
2151 tttttattct gagatttctg cctttctgt tcttttgc gagcctaact  
2201 gactgagttt caatatacag ttctgaaagc aagtgagcat acttagtgc  
2251 atgcaatgtg cacagaaaaga tgttggttcc tacctctcaa agctcacc  
2301 aggatattac tcatattgcc acaaagtaca tttacaccaa taacacatac  
2351 tttggtaatg ggaaaaataaa ataatcttag gtaataaaat gcactttgt  
2401 gcttataaaag gaaaataatc atcacaggta gaagaggagg aaggcaagac

### Exon 1

## Exon 2

FIGURE 1B

FIGURE 1C

6601 aagtctgtc acgcctcac aaccacctc gtgcagcaat gattctgtaa  
5651 atatccatgt gtcctcaaca ccaggtaaaa tttagtccctt tggtaaaaaac  
5701 attcattccc tcaaattctc ttccaataca ctaatatacc ttcccaaaaa  
5751 gtaaggagaa gttgaaagc tagctggatt gatgatggta tgcgtatgtc  
5801 tataagttat agttagtaag catgttttta ggatattttt ctgcctcca  
5851 aagagacaca attccggaag atatttactt ttgtgtatcc ccacattttg  
5901 gtttaagttt ggagccatct cttagatctt atttcattcc ctaataatgt  
5951 gttatactag tagaattttc caaattacat agaattataa ctgcaactct  
6001 tctgactgtat gcctttttt tgcattttat gatgcagttt acatcacaaaa  
6051 ttcttcctt gcagggatta tgtaaagagg catgttgacc tgctagccct  
6101 atgttacttt aagtatatgc acacacacaa aaagaacaa aaacagctgg  
6151 gaattgatta tggtgatatt ctgaataaaa gcaatagttc taattatgtta  
6201 tgtctaatta gccacagctc ttcaagaatt gctgaaatg tcacagggtt  
6251 tataatgtcg gcatttcattt ttcacgaaaaa tgctatttga tggcataaaaa  
6301 ccagaaaaaa ctaatggtca cagaagacag cttgttagatt agacaaggt  
6351 cactgtgtt taatgaacag tgctgttaat taatgagaaaa acaactggta  
6401 catgagctt taagcattgt gaatttgcattt ccaaaaaatc aatctgccta  
6451 aaacaattt aagttagctaa aaaacaaaaat aacggcaaga acataattta  
6501 aacctcaaat ggtacagcag agttatatgt atcaattttaa ttgaatcaca  
6551 gttctcaggt gtgacatatg aagaggctt tttaatgcct gaaaaagaggg  
6601 gttaatatgg attggatttc tcaatacata ttgttagataa aattcaagac  
6651 tagctctacc actgcctttt ttctttttt tttttttttt ttatttgaga  
6701 cagtatctcg ctctgttgc caagctggag tgcagtggca tgatctcgcc  
6751 tcactgcaag ctccgcctcc cgggttcaag ccatttcctt gcctcagccct  
6801 cctgagtagc tgggactaca ggccccccccc accacaccca gctaattttt  
6851 tgtatTTTTt gtagagacgg ggttccacctt tattagccag gatggctcg  
6901 atctcctgac ctcgtgaccc accccctcg gcttccaaa gcgctggat  
6951 tacaggtgtt aaccaccccg cccggccacc actgcctttt aggcttttta  
7001 atttccattt cattaagaa gaataagaaa atgttcttat gtttaccaa  
7051 aattctgtga ggacaaatga ggaaccattt taaactccttac aaggtagt  
7101 ataaaaataaa tacacattt ttgtcttgc ttttgtttaag agttatccaa  
7151 gccaagcttcc taggggcttta aataaggaag gacaggacca ttgttataaa  
7201 catcaagttt ccactacagc tttcctccaa acaagtcaaa tattctgaat  
7251 attattcact aatctctttt gctgcccattt cagtaatag cgagcatttt  
7301 atttcaacta aaaccaagca agagaaaaatg aactgccttta tcctgaggt  
7351 cagcagcaaa ggcaccagaa cttgtctcat ggcttaccca gcaagggtca  
7401 gaagaaccat ccctaattt aatcatctcg actgaatgtt acaagatttt  
7451 gtatTTTCAA ctcatatgaa aataaaaaacaa tgagacctca tccaaagggt  
7501 gatTTAGAGA gtacccctaa acaaaaaacaca gtggaaatag acccagcatc  
7551 tggatttggaa gaacacattt cctcttacga gtctatccca ttgtcttagat  
7601 tgctggcaat ggctttttt aattttaaattt gttatttgaga taattgtaga  
7651 ttcacatgca gttgtaagat atagtagaca taccctgtgt atacttacc  
7701 caatttccgc aaaaggttaac atttgttaaa actatagtat aatatcaca  
7751 ccaggataat aatattgata cagctcacaat atctcattca gatttctcca  
7801 gttttacttq aatacatttq ttttttttttq ttttttttttq ttttttttttq  
7851 ttttttttttq aatacatttq ttttttttttq ttttttttttq ttttttttttq  
7901 aaacaacaat caagatatttq gacagtccq gccccccacg gtggctcaact  
7951 cctgtatcc cagcacttttq ggaggcccg gcaaggccat caccagggtca  
8001 ggagatcaag accatcttgg ctaacacggt gaaaccacgt ctctactaaa  
8051 aatgcaaaaaa attagctggg cgtgggtgtt ggcgcctgtt gtcccaagct  
8101 ctcgggaggc tgaggcaggc gaatggcatt aaccaggggag gtggagcttq  
8151 cagtggcccg agatcgacc actgcactcc attctggca acagcgcgg  
8201 actctgtctc aaaaaaaaaaaa aaaaaaaaaaa gatatggac agttccatttq  
8251 tcacaaggat ctctcaagttt acccccttgc aaccacatcc accttcttct  
8301 tcacacttgc acaccccttc cttctccat cctgacccca gcagccacta  
8351 atctgttctc catttctgaa atgtttttt atgtttttt tttttttttt  
8401 ggaataatac agtgtataac tttttttttt tttttttttt tttttttttt  
8451 ataattccct ggcaattcat ttatgttact ctgtgtatca atagttcatt  
8501 catttttattt attgaggtagc attccatggt atggaggcac cagagttgt  
8551 ttaaccatcc tcatggtgaat ggacatctgg gctttttttt gggctgggt  
8601 attatgaata cttttttttt gAACATTCTTAC tttttttttt  
8651 ataagtttcaatgatctctgatca caccatggcc caagagtaca attgctgagt  
8701 catatggtaa ctatatgttcc agttttataa gaaacgacca tgctcagaag

D6S280

FIGURE 1D

8751 gaccatactg ttttacattc ccatcagcag tggtaatg atccagttc  
 8801 tccgcatect ccccgccatt ttgtgtgtc actatttttt gccactattt  
 8851 tttatTTAG :cattctgtc agctgtgtag tgataccatt gggatctaat  
 8901 ttgcattttt ctgatggcta atgatgtcaa ataacttttcc atgtgtttct  
 8951 ttgcacatag tgtaacttct ttatgtatg tcctctttt tgaatatect  
 9001 atttatacct ttgccaattt tctaatttag ttttgggtt tttactgttg  
 9051 agtttaagg ttcttaca tatttagat attagtcctt tgcagat  
 9101 gtggtttaca aacattttct cccagctat ggcttgtctt ttcatcctta  
 9151 gtacctgggc tctcacagag taagttta ctttgcattt agtccaaattt  
 9201 ctcattttt cttttataa cttctgttt tgatgtcaag attaagaact  
 9251 ctttgccttgc tccaaatccc aaaaatatct cattttttt cctaaagg  
 9301 ttattatTTT atgttttaatt tttaaaccgg tggccattt ttaaatgatt  
 9351 atcataagat aggaagtata gattaaggc cacttttttgc cctatagatg  
 9401 tccaaatTTT ccagcatcat ttgttgaggcc ccccttttcc tccattgaaa  
 9451 tgctttgc cttttaaaac aatcaattt agcatattt tgggggtct  
 9501 gttctgaatt ctctattctg ttcaactgtt tataatgtctg tatgttccat  
 9551 atgtctatcc ctccaccaat ccacagtctt gattactgga gctataatag  
 9601 taggcattaa tattcaggtaa agtgcatttgc cttcttttgc tcttcttgc  
 9651 cagcattgtt ttagctattt caggttctgtt gcattttccat ataaatttt  
 9701 aaataagttt gatatctaccc cccaaaaaaa actttgcgtt gattttgaca  
 9751 ggaattttat tagacctgtt gatcaatttgc gaaagaattt acatcttgc  
 9801 tatgatcattt cttccaaattt ataaacacgg tatttcttcc cacttattt  
 9851 ggtcttttgc gatttctttt atctgcattt cataatctca atgcacataa  
 9901 accgtatgtt ttttctaaag tggatatttgc agtttattttt atttggaaatt  
 9951 attataaata ataaatttttgc gtttcttattt ttcattttccat catgatcatt  
 10001 gtttagatattt gaaatatttgc ttaatttttgc tatttgcattt acatgtgc  
 10051 gctttgttgc actacttttgc ttcaagagttt ttttgcgttgc ttttgcgttgc  
 10101 ttttctgttgc gaccatcatgc ccattttgttgc atagagacca ttttgcgttgc  
 10151 accttccaaatccatgc ttttttttttgc tatttgcgttgc ttttgcgttgc  
 10201 actatttataa taacttacaa tactatgttgc aataagatgttgc atgaaatgtt  
 10251 acatcttgc ttttcttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10301 taagtatgttgc gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10351 taaaccttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10401 gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10451 tagctttattt atataatgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10501 gctttgcata ctttgcataatccatgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10551 ctgtttgcata atattttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10601 atatgggtat gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10651 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10701 ctccttattt ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10751 aatgttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10801 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10851 accttgcatttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10901 aatgttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 10951 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11001 ccccttatttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11051 gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11101 gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11151 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11201 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11251 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11301 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11351 agttcaattt ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11401 ctggaaatgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11451 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11501 gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11551 ataaatcttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11601 tgctgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11651 ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11701 tatgcccata gtttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11751 tacgacttaa ctttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11801 tatgatatttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc  
 11851 aatgttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc ttttgcgttgc

FIGURE 1E

### Exon 3(D)

FIGURE 1F

15051 ccacttatta aaccagaatt tatggaaatg tggctgtgtg tgaggcactg  
 15101 gtgttacaat agtgaatcta gtggattct cagttaaatc tatctaaaaa  
 15151 taccttgttt ggccctcacg aatgcagtc gtttgcgtt cttctccat  
 15201 aataggctt actgccttt ggaagccatc atgctaaggat atggagcaaa  
 15251 gtcgggtgtt actccaaggc ttgcagggtc ataaaggcccc aaggcatatt  
 15301 agtgaaggca ttagattttt ctccctggag atgtttttt ctctctgaat  
 15351 tctctactca ggcagcatta caaaggactg taacctgtat tgaaactact  
 15401 gcacaacaag tactttctgt cccataaggg gccaaacaa aacaattcac  
 15451 aaggcagatg gttagccaa attcactcaa cttctacagg ataaggtcag  
 15501 ttcatggatg actggaaaaa tgtttcatc cagattttaa aaccaattaa  
 15551 aaattggttt tgttccaaatt tcagaagcaa tgccatgtt tctctggcct  
 15601 ccatgcggaa aagaaagctt tttcccagat gtctgctgcc ttttgatagc  
 15651 tgtttccatc tacggataca tcaacacatc ttagtcctt agtcttcctc  
 15701 ttccctgcctc agatccttgc aggtcttgat ataatatgtt gttctaaaaa  
 15751 ttagttagtgc ttatctataa tcttacttgc ctttggatgt atcaatagt  
 15801 acctaaaaaa ttttagtataa tgcctggcgc agtcaactct gcctgtatc  
 15851 ccagccctt ggaaggctgaa ggaaggcaga tcacttgagc ccaggagttt  
 15901 aagaccagcc tgggatggaa agacctgtct ctacaaaaat ttaaaaaattt  
 15951 gctgggcattt gttccatataa ccttgcgttgc cagttactca gaaggctgag  
 16001 actggaggat catttgcgc caggatgtt aggctgcgtt gagccatgtt  
 16051 cctggccacta cactccagcc tgataaaaa gatgttgcgc ctgtctcaaa  
 16101 aaaaactatc ttttgcgttgc ttacgcata attgcgtttt ttttgcgtt  
 16151 tcagacccctt tctttatc ttttgcgttgc ttatccatc ttttgcgtt  
 16201 tggaaagaaaaa ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16251 gtcttagatc ttatccatc ttttgcgttgc ttatccatc ttttgcgtt  
 16301 attaaatgtt ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16351 aagcatgttc aaatgtgttgc ttttgcgttgc ttatccatc ttttgcgtt  
 16401 acacaaagga atcaaacatc accttcctgc ttttgcgttgc ttatccatc  
 16451 tgactgttgc gacttttgc ttttgcgttgc ttatccatc ttttgcgtt  
 16501 tgatgttgc gtt  
 16551 cctaaatccatc ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16601 cctgataact ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16651 aaacttcatc ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16701 acccaaataat ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16751 gattgtggta gactggctgttgc ttatccatc ttttgcgttgc ttatccatc  
 16801 cacaccaatg ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16851 ggtcagctaa caagccccat ttttgcgttgc ttatccatc ttttgcgtt  
 16901 attgatagat ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 16951 tctgaaactgc ccaccccttgc ttttgcgttgc ttatccatc ttttgcgtt  
 17001 att  
 17051 gtt  
 17101 ttt  
 17151 atgtatgttgc ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17201 tatcttagaaat ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17251 ctt  
 17301 attgtgttat ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17351 caagctgc ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17401 gaaaaacacaa aacactcacc caataacatc ggcataaaaga atttgtgaat  
 17451 aaccccttcaatg ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17501 gacccatccaa aaaaatgttgc ttttgcgttgc ttatccatc ttttgcgtt  
 17551 taatgagccat ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17601 ttt  
 17651 ttt  
 17701 tagtcttgc ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17751 att  
 17801 ggaataaaaat aaaaatccatc ttttgcgttgc ttatccatc ttttgcgtt  
 17851 gccttttatttta aaaaatccatc ttttgcgttgc ttatccatc ttttgcgtt  
 17901 attttccatc ttttgcgttgc ttatccatc ttttgcgttgc ttatccatc  
 17951 gatcgactc cccaaaactgc cactgtgttgc ttttgcgttgc ttatccatc  
 18001 att  
 18051 ttcaatggca ttatccatc ttttgcgttgc ttatccatc ttttgcgtt  
 18101 aattatatt  
 18151 ttt

FIGURE 1G

18201 gtgattaact ggaccatctg aggacaatta aaacctgtt gattggctga  
 18251 tcacaaaaca taaaacaat ttaatccct ctagtttagta atagctgata  
 18301 tttattgaga actactataat attaggtact actttaagca ctttataaaat  
 18351 atggctttat ttaattctac ataagtacta taatgtcctt atttattttta  
 18401 ttttatttttta ctttacttta ttttattctt ttttattttta ttttattttta  
 18451 ttttattttta ttttattttta ttttattttta ttttattttta ttttattttta  
 18501 ctctatcacc caggctggag tccaaatggc atagctcag ctcactacaa  
 18551 cctccgcctc ctgggttcaa gccattctca tgcctcagcc tcccgagtag  
 18601 ctggactac aggcacacgc caccacaccc agctaatttt tgcatttta  
 18651 gttagagatag gatttcaccc tggccag gctggctt aactctggc  
 18701 ctcagaat ccaccgcct cagcgccca aagtgcgtt attacaagtg  
 18751 tgagccacca cgcctggcct ttataatgtc ccattttata gatgaggaag  
 18801 taagacaaga ctgaagactt tatagatgag gaagcaagac aaactaaaaa  
 18851 agatgatagg tgaaagaacc tggatttatt tctcatgatt tcactctaga  
 18901 aaaatataca taccctactg gaaaattgtc tttactgttt attagcattt  
 18951 taaaattaaa ttaattgaa ctttatctat tgcattcaac ttgttaaacag  
 19001 aagaacatga tactattatg cttatcatta gtaattcaag atctttaaag  
 19051 aaaagccagg ctttatagaa cattaattgc agtatacagcc ttaatttatat  
 19101 caactaaattt atgttaccta ttgctgtct ctaacctgaa tggaaattta  
 19151 ggacctaataa tagacttact tacctgtatc aaacttgcattt atactctca  
 19201 gttgttgtta tcatgaggtt ccctgtgtat ttccaaattt gagaccccttg  
 19251 gagagcaagt aacattactc gcaggactac cttcaaatgt tttttaacat  
 19301 taataaaacta tcggtaattt agataattgt tgacctggta cacaacttg  
 19351 aaagttgaac ttacaagaca gctttaggtt ctgatgtt tggaccacat  
 19401 gaagaaaattt tatttccgaa gaggaaaatg aataaggattt atttcccact  
 19451 ctttctataa acttttagtag agcactatga tatactgtat taacattctg  
 19501 tactatcaca ttttacataa gaaaattcat tcacagacag ggtatttatt  
 19551 atgtgtcaaa cataatctta agtataaagg atacaaaaagc gactaaaaca  
 19601 cggccctcgc ctgtaaagat agaatctcct gtgccttag agaatggcaa  
 19651 aactaaagg aggtataacta taattatgtt gttacagagc aaaggtgatg  
 19701 gaaattgaag tagtcctaga aagaaggcta tggaaatataca tgagtgttgg  
 19751 tataaaaacaa agaagcaag gactaccccc aggtttcaa attatgtttt  
 19801 agtcatccac tgaacattta tacaatttctt accatgttcca agcatgttta  
 19851 tggatgctgg agaggctgtt tggcaccaaa tggcaaggtt cttcccttctt  
 19901 atagagataa tattcgtgtt gacaaagaaaa aacaatacacaa aatatgttt  
 19951 ttgaaaaaca agataatgtc atctacagat aagcacaatg aagaaaataa  
 20001 aacagaaaaga gtagaggcta ctttagctt ggtggcttga gaaagtctt  
 20051 ctaagtagtt gacacttgat ttgacctgaa tattaaagaaag aagccagcca  
 20101 tgaggaggat tagacacaga tcttccagg ccaggaaata gtaattgcaa  
 20151 ggatttttaa cacttgcata gcttgggtt tacaagggtt agacataagg  
 20201 tctcgtggct ggagcttaat gacgttggg gagaatagca gaagggtata  
 20251 ggggagacag cgcagggtca caccctgaag gccatgttagg ctctgttacc  
 20301 ctgaatcaag gttccttctt aagacaggcc accaggcaaa ggtccctacgg  
 20351 gttgctggca ggcctaataat gaatactt caggttataa acagcagcat  
 20401 taatcaggca aaaaaaggta tggctttta atgccttggg ttttttagtc  
 20451 atgtatgcct gttggaaactt catatcagca atatacaaat tattaccat  
 20501 ttatgtttat aaaaaacata aacataagtt tataaggaaa taatcccttg  
 20551 aattttgttt ctatattttt gcccattaa acatgaaattt ttacattgtt  
 20601 ttttaaaatg ttatttttctt atgaggaactt ggaatttagaa tggatggaa  
 20651 actttttttac agccccagtg gtatcaccag taagcagttc ctaagatcct  
 20701 ccttgccttcaag ggactcttattt ccatacttctt agttatgtt attgcagtg  
 20751 agaatttattt cattaaagat ttgttattttc tttttagaaaa ttgtcccttt  
 20801 ttgccttggat atgttattctg aaactgtatg atcaataaga agcattaaac  
 20851 tgtcactatg gggtaaaattt tcaaaatgtt gcttgcattt tgccagttt  
 20901 agtcccattt acttctgtgg aagtcttgcata gttttttttt ttttttttt  
 20951 tttgaaaatg ttctacaatgt ttgttctttt ggtgcctttt ttatttttaa  
 21001 taaaatatcac agagcaactc agtgcataatgtt gatttgcattt atttaaagaaac  
 21051 gtggataatg tactgtgcag gaggagactt taaaattttt atttaaagc  
 21101 ttcatttctt ttaagatgtca caacaacaat ataaatacatt ctttagttt  
 21151 tcaaagagca ctttctataa aaggaattttt gagctcaattt agaataataga  
 21201 gcttataaaag cagcaccatg tccctctgag acattgttta cttcactctt  
 21251 tagatggaaa agtgcaggca ctgtgaagtg ggggtgcattt gtccttagcc  
 21301 cataaaatcag cagtaaaatgtt aggaatagca tgctggccctc ccaatagctc

FIGURE 1H

21351 attgctctaa agcaactgcct cttgttagag tcaaatttaa ttatagtata  
 21401 atccgtttaa tctacatgtg gagaataat gaaggagca gaaaaatgaa  
 21451 tttcttaaca gatcagtgg aaaccatatt acatagatta gcaactgtct  
 21501 tttcaagatc cgtatittcg gcatgtacta gatggtatct gatgcattga  
 21551 aagcaaataat tctaattcca ctggccagaa ctggcaaaga acttcttatt  
 21601 ttcctcactt taaaacataa gtaaaggggg tccacttcaa aattataaag  
 21651 ccatgtgata tgattcgatt cctgtccca aatctccctc cttctagggg  
 21701 ccattgtcta aagtctaaa gaaaacatac caggcacagt ggctcatgcc  
 21751 tctaattcca gcaacttaaa gggagagca ggtaggagga tcacttgac  
 21801 ctaggagttc aaaatcatca acctggcaa cataatgaga ccctatctct  
 21851 aaaaaaaaaa caaaacaaaaa caaaaacaaa caaaaaaaaaac tgtaatagct  
 21901 ggggtgggtg gaacacactg gtagtctcg ctactcaggaa ggctgatagg  
 21951 agaaggtaac ttctgcccag gaattcaagg ctgcagtgaa ttatgattgc  
 22001 accactgtac tgcagcctgg gcaacagagt aagacagaga gagagaaga  
 22051 caaagagaaa ggaagggaagg aaagaaggaa ggagggagg aaggaa;gaa  
 22101 ggaagggaagg aaggaaggaa ggaaggaaagg aaggaaggaa gggaaagaagg  
 22151 aaggaaggaa gggagggaagg gagggaggaa aagaaaggaa aggaagaaaa  
 22201 ataaatgtaa ctattataaa agatgttcaa ttttttattt tggaaataact  
 22251 ttagacttac tttagaaggta caaaaatagt acagaatttc catgtcaaa  
 22301 tgtactctt acctaacttt ccccaaataa ttttacctac gtataactgca  
 22351 attatcaaaa ccaggatatg aatacataact attagctataa gtctttattt  
 22401 gaatttcacc agtttttaca tgcgtcaat ttttataatac actccataaa  
 22451 aattttctca catgtatata tgcatttaac caccaccaca atcaaaatac  
 22501 aaaacatttc catcaccctta aataaaacttgaatgatata ctttgttatta  
 22551 ttcctttaca ggtactccct ctcttcaatc ctaacctctg ggaaccacta  
 22601 tatctgttct gtttcaactgt aattttgtca ttttataataat gttatataaa  
 22651 tggaaatgtaa agtagtaat tttttgaaat tggcttttc ttacacagca  
 22701 tgatgtctt gagatccatc caagtgcatt aatagtgcatt tcctgtttat  
 22751 tgcttaatag aattccatgaa tctagatgtaa acacaatttgcatttatt  
 22801 tacctaatac aggtcatttgc ggctgtttct agttttggc tattacaat  
 22851 aaggcagcta tgcatttca tgcgttaggtt tgcgtatgaa cgtaagttt  
 22901 tatttcttaa gggcatataa gtgcgttttc acctttatca gaaactgcca  
 22951 aactatttcc ttttaaaaata tagaaatgcc aatgcacaaaca tgcgtatgga  
 23001 ggtcagcagc cccacccctt gccccacgct gccactgctg ccagtgtaa  
 23051 catatgcattt gaggctggca gccccacgct caccactagc ctgccccctgc  
 23101 actgcacactg ctaccagcat gagegtgcac atggaggccg gcagcccat  
 23151 ggccaccagc actctgcccc agttgtatgag cattcaccacc accacactgc  
 23201 cacttgcctt tggcaactgt ctggcactt acaaatacgac acagatcctg  
 23251 ctgccaccac cccaaacaaag tggttggct ggcaccaccc atcagagtat  
 23301 tgcgtttccaga ggtcaggaa caccttagcg cttccactt agcagtttcc  
 23351 taacccatcaag gggccagaga ataaagtctg agatccagta acagccctccc  
 23401 aaagtgcag catacagccc aaaaggctcg agctgagctt tacccttaaa  
 23451 attctccatc aatgaagcc agtcaactga accccaccta tatgagattc  
 23501 aaacccatca gggcatcaaa gaagatagag gaaaaaaaaaaaaaaaaaaaa  
 23551 aaaaaaaaaacta tccaaaggac agcaatttca aagactgaag gaaaatcagc  
 23601 ccacacatgataaagaagac cagtgcaga gctctggcaaa ctcaaaagtc  
 23651 agatgttctt cttacccatca aacaactgcgt agtgcgttttcc agcaatggtt  
 23701 cttaaccagg ctgaaatgac aaaaagagaa atcagaatgt ggataggaaac  
 23751 agagatcaactt gagattcagg agacagtgaa aacctaattcc agggattctt  
 23801 aggattacaa caaagtgtata caggagatgaa aagacgaaat ggccacttta  
 23851 agaaagaaca gaaactgtatc gatagagctg aaaaactcac ttcaagaatt  
 23901 ccagaataaca atcacaaata taacggcaga atcgatcaag ctgagggaaag  
 23951 aatctcagag cttgaatatac gcttcctgtt aataactcg tcagacaaaa  
 24001 ataaagaaaaa aagattaaa gaagaatgaa caaaatctcc aaagtatggg  
 24051 attatgtaaa gacaccaat ctatgactca ctgtatgtccc tggaaagagag  
 24101 ggagagaaaag caagcaactt ggagaacata tttcaggata tcattccatga  
 24151 aaattccccc aacttcaacta gagaggccaa cattcaaaattt gagaatgc  
 24201 agagaaccct tggatgatc tatacagata accatccccca agacacatac  
 24251 ttgtcagatt ctctaaaggc aaaaacaaac aaaaaatgtt aacagcagct  
 24301 aaagagaagg ggcaggccac ctcccaagga aacccatca ggctaacagc  
 24351 acacccatca gcagaaactc tataagccag cagagatgaa ggacccatata  
 24401 tcagcattat taaagaaaaa aattccaaa caagaatttc atatccagcc  
 24451 aaactaagct tcataataatgaa aggagaaata agattcttt caggcgagca

FIGURE 11

24501 aatgctaagg gaattcatta ccatcagacc tgccttataa gaggtcctaa  
24551 agagagtgtt aaatatggaa agggaaagatt attactggca actacaaaaaa  
24601 cgtgcttaag tacacacacc attgatgcc aaaaagcaacc acacaaacag  
24651 atctgcataa taaccaatta acaacacaaa acaggattt atccctcaaa  
24701 tccacacata tcaatattaa ccttaatgt aaatggcata aatgcctaa  
24751 taaaaggcac agagtggcaa gttggacaaa gaagcaagac ccaacagtat  
24801 gctgtttga atagacccat ttcacatgca gtgacgcaca taggatcaaa  
24851 ctaaaggat ggagaaaaat ctaccaagca aatggaaaac agaaaaaagc  
24901 aggagttgtt attctacatt caaacaaaac agactttaa ccaacaaaaa  
24951 tcaaaaaaga taaagaaagg cattacataa tggtaaaggg ttcacctca  
25001 aaggccagac ttaactatcc taaatagata tgcattccaa acaggagcac  
25051 ccaattcat agagcaagg ttagacacc cacaagaga tttagataac  
25101 cacacaataa tagtgggaga ctttaacatc ccactggcag ttagacag  
25151 gtcattgagg cagaaaaacta acaaagaaaat ttagacccat gtttgcac  
25201 ttgactaaat agacctaata gacatctaca gaaatctcca cccaaaaaca  
25251 ggagtgtata tattcttctc atctgcacat gcccataat ctaaaattga  
25301 ctaatcagcc ataaaacaat ctttagcaaa taaaaaaaaa tcataccaac  
25351 cacactctca gactacagtg caataaaaaat agaaattaaat gaaaaattaac  
25401 ctgcttctga atgacttttgg taaaacaat gaaattaagg tagaaattca  
25451 gaaattattt gaaactaatt agaacaaga tactacatac cagaatctt  
25501 gggacacagc taaagcaata ttaagaggaa agtttataga gctgaatgcc  
25551 tacatcaaaa agtttagaaag atcttaagg aacaaccgaa catcacacct  
25601 agaggaaatc jagaacaag agcagatcga ccccaaagct agtagaacac  
25651 aagaaatcaa aatctgcact aaactgaagg aatttgagac gaaaaaaaac  
25701 atacagaaga tcaatgaatc caggacttgg ttcttcgaaa gaataataa  
25751 gatagataaa atgettagcta gactataag gaaaaaaaaa gagatcaaaa  
25801 taaacacaat cagaaatgac aaaggatgt taccacctac cccacaaaaa  
25851 tttaaaaaac cctcagagac tactaaaaac acctctatgc acacaaacta  
25901 gaaaacctag aagaaatgga taaattcctt gaaacataca accttccaaag  
25951 attgaaccag gaagaaaattt aatcttggac agagaccaat aatgagttcc  
26001 aaaattgaat cagtaataaa aagcttacca accagaaaaaa gcccaggacc  
26051 agagggattc acagctgaat attacaagaa gtataaaagaa gagctggtac  
26101 cattctact gaaactattt caaaaaaaaaag aggaggaggg actccttcc  
26151 aactatgaaa ccagcatcat cctgatcca aacacttggca gggacacaac  
26201 aacaacaaaa aacaaaactt caggccaaat ctttgcataa catagatgca  
26251 aaaattctca ataaaatctt agtggaaatga atccagcagc acatgaaaaa  
26301 gctaattccac cactatacaag gagggttcgt ccctgggaca caagtttgg  
26351 tcaacatata caaatgaata aatgttattt acatcataaaa cagaattaaa  
26401 aacaaaaacc acatgttcat ctcataaaaat gcaaaaaagg ctttgcataa  
26451 agttcaacat cccttcacgt taaaaaccctt caacaaacta ggcactgaag  
26501 gaacatactt caaaaataata agagccatct ataaagaaact cacacccaac  
26551 atcacagtga atgagcaaaa gctggaaagca ttcttattaa acacccagaac  
26601 aaaacaagga tgccttctt caccagtctt tttcaacata gtactggaaag  
26651 tcctggccag agcaatcagg caagagaaaag atataaaaagc catctgataa  
26701 gagggaaagt caaactgtcc ctgattccag tcaatgtat tctatgccc  
26751 gaaaacccca taatctctgc tccaaagctc ttgggtttga taaacaactt  
26801 cagcaaagct tcaggatata aagtcaatgt aaaaaaaatca gttagatcccc  
26851 tgcaccaaactt caacatccaa gctggagggc aatcaagaa tgctatcccc  
26901 caagctgcc accatggcaca cttacaaaactt ggtgcagatc caqccacqeq  
26951 agagtgatgtt gaaaccttggq accacttca cqgggttggta cqacccatcc  
27001 ctgagcccaag cqggccatca qggggcaaaq cggccacttc qgatgttgg  
27051 ctatgttccatcataatcttccat tcacccatcatt cccaaagaga qcqatcccc  
27101 ctttctggac agtgcataat gccatgtatc agatotatctt qccaaatgt  
27151 aqgacttggc ccctcaatca qccagactat qgggtcttag ccqgtctca  
27201 taaaaccaaa actgtgtccaa aacatagtga aqcccaaggtq aqatctgca  
27251 ggtgttccat tttatgtccca ccaccccttccgaa tggagccctt ccatecttcc  
27301 tacagcaaca tcaatgttca qccacccatca qccacccatca caaaaaatca  
27351 ccttccctcc totgtatgttcc tttatgttccca qccatgttcc  
27401 tttgtatgttca aqaaatgttcc ccccaatgttcc aqggggggggaa atqgggtactt  
27451 actqcaqcccttccatggccaaacttccatccatccatccatccatccatccat  
27501 ttt  
27551 ttgttt  
27601 agtttccatccatccatccatccatccatccatccatccatccatccatccatccat

**Phosphoglycerate  
mutase,  
processed  
pseudogene**

FIGURE 1J

27651	ccccaggggca	aaagccaagaa	gtgaaggccca	gcaaacacggc	accctccctgg
27701	cccatggcat	ccatctgtcc	ctccctccctg	aacatgtcac	actgaccaca
27751	tctatagaca	tcttgagggtt	cagctgcaga	tggggacccgg	tggctcccat
27801	tttcatttta	gccattttgt	cttctgcacc	cactcccttc	atacattctta
27851	gtcagaatag	caacttctagg	gcacagggttc	tcagtcataag	ctgtggaaaa
27901	gcccccgta	tccaaagagag	ttcaaagata	gtgacttggg	ttttgcaag
27951	tgcattgtt	actaaggact	tgtgaggagg	agccatgctg	agctacgacc
28001	aatgaggaga	agcaagagag	cctgtctgcc	cccaggagct	agtctgtgc
28051	ttgtctgtag	tcagggccact	gcctggggc	tctagtcatc	ccagtggaaag
28101	atgaatgtaa	cctgcatgtt	gatgtgacag	ctgtttccctc	cctgacccca
28201	ttacattttac	ttttatttaa	aaaaaaaaaa	gtatagtgta	tataaataat
28251	acaaaacaat	aacccttcta	agggttctc	gtggtggttg	aaatagtccc
28301	acatgtggtc	atcagaacat	aaggccattcc	tcataccaat	atggggtaag
28351	ctcccttgacc	tttgaggggc	aggagtgcct	catgctgtgt	gttttagaat
28401	ccctccctgc	cttgtttcat	ggcagtgaaa	tgcctcttgg	tcctctccaa
28451	gtgtgtttt	cactgattt	tgaatcatgt	tgcagttgtc	tggccctgccc
28501	acataggctt	agtgttcat	tgagcataac	tgtactaaat	ccttttcca
28551	gatcagtata	ataaaaggagt	gatgtgcaat	aaaaaaaaaa	atgcccattccc
28601	atgcacacca	gttagaatgg	tgatcattaa	aaagtcaagga	aacaacaggt
28651	gctggagagg	atgtggagaa	ataggaacat	ttttacactc	ttgggtggac
28701	tgtaaactag	tccaaaccat	gtggaagaca	gtgtggtgat	tccttaagga
28751	tctagaacta	gaaataccat	ttgaccacgc	catcccatta	ctgggtatata
28801	actcaaagga	tttataatca	tgctttata	aagacacatg	cacatgtatg
28851	tttattgcag	cactattcac	aatagaaaaag	acttagaacc	aacccaaaag
28901	tccatcza	atagactgga	ttaagaaaaat	gtggcacgta	tacaccatgg
28951	aatactatgc	agccataaaaa	aaggatgagt	tcatgtccctt	tgcaagggaca
29001	tggatgaagc	tggaaaccat	cattctcagc	aaactatcac	aaggacagaa
29051	aaccaaacac	cacatgttct	cactcatagg	tgggaattga	acaatgagaa
29101	cacttggatg	cagggtgggg	aacatcacac	actgggcct	gtcatggggt
29151	ggggggaaagg	ggggagggtat	agcatttagga	gatataccga	atgtaaatga
29201	caagttaatg	ggtgcagcac	accaacatgg	cacatgtata	catgtgtaac
29251	aaatctgcac	attgtgcaca	tgtaccttag	aacttaaagt	atagtaaaa
29301	aataaataaa	taaataaaaa	tttaaaaaat	gaataaaaata	catagaaaata
29351	cagctaacc	ggtaggtgaa	agatctctac	aacaagcatt	ataaaacact
29401	gctcaaagta	atctgagatg	atataaacaa	aaggaaaagc	attccatgt
29451	catggatagg	aagaagcaat	attgtttaaa	tggccatatt	gccccaaagca
29501	attacagat	tcagtgctat	tcctatccaa	ctaccatgtc	ttccacagaat
29551	tagaaaaaaa	aattattaa	aaatttgat	gaaacccaaa	aaaaggctga
29601	atagccaagg	caattctaag	caaaaacac	aaagccagaa	gtatcacatt
29651	gtgtgactic	aatctatatt	acaaggctac	agtaaccaca	acagcatgg
29701	actggtacaa	aacacataga	ccaatggAAC	agaagagata	gccccagaaat
29751	aatggccacac	acaaaccatt	tgatcttaaa	caaaccataac	aaaaacaacg
29801	aatgggaaaa	gaaattccta	ttccataaaat	ggtgctggga	taactggcta
29851	gccccatatgca	gaagattgaa	attggacccc	ttgtttatac	catatacaaa
29901	aatcaactca	agatgggtt	aaggcttaaa	cataaaacct	aaaactggcc
29951	gggcacgggt	gctcacccct	gtaattccag	cactttggga	ggccgaggca
30001	ggcggtatcac	gaggtcagga	gatcgagacc	atccctggcta	acacgggtaa
30051	acgccatctg	tactaaaatt	acaaaaatt	agctggcga	ggtggcgggg
30101	acctgttagtc	ccagctactc	gggaggctga	ggcaggagaa	tggcgtgaac
30151	ccccgggggc	ggaggctgca	gtgagccgag	atgctgccac	tgcaactccag
30201	cctgggcgac	agcgagactc	cgtctcaaaa	aaaaacaaac	ctaaaactat
30251	aaaaacccctg	gaagatgacc	tggaaatac	cactctggac	atataggacc
30301	tggcaaagat	tttatgacaa	agacaaaagc	gattgcagca	aaaacaaaaaa
30351	ttgactaatt	ttgtcaatta	aactaaagg	atctaattaa	actaaacagc
30401	tttcgtcacag	aaaaagaaaac	tatcaacaga	gtgaacagac	aacctacaga
30451	ataggagaaa	atatttgca	actatgcata	tgacaaaagg	ctattatccg
30501	gaatctgtaa	ggaattttaa	caaattttata	agcaaaaaaa	caaacaacac
30551	cattaaaaaa	tggcaaaagt	ccttgcacag	acactttta	aagaagacat
30601	acacgtggcc	aagaagcata	taaaaaaatg	ctcaacattt	ctaatcttta
30651	gagaaatgca	aataaaaacc	acaataagat	accatctcac	aaaagtca
30701	atggcttatt	ctaaaaagtc	aaaaaataac	agatgtggc	aaggtttatgg
30751	agaaaaagga	atgcttata	actgctggtg	ggaatgtaaa	ttagttcagc
30801	cggtgtqgaa	agcccttgg	caatttctca	agaactcaa	aatggaatta

FIGURE 1K

30851 ccatttgacc cagtaatctc actattgggt ttattctcaa aggaatgtaa  
 30901 ctcattctac cttaaagaca tatgcacta tatattcatc acagtactat  
 30951 tcacaatagc aaagacatga aatcaaccta catgccatt gatgggtggat  
 31001 tggataaaga aaatgtggta catatacacc ataaatacta cacagccata  
 31051 aaaaagaaca agatcatgtc ttttgcaca acatggatga ggctggaggc  
 31101 cattcaccta agcgaactga cacaggaaca gaaaaccaaa tacacatgtt  
 31151 ctcacttaca agtgagagct aagcattgag ttatatggtc acaaacaaga  
 31201 gaacaacaga cgcgtaaagcc tacttgagga tggaaagtgg gaggagggag  
 31251 agcataaaaa aactacctat caggtaactat gcttttacc tgctgtatga  
 31301 aataatctga acatcaaacc cccataatata acaattcacc tatataacaa  
 31351 acctgcacat gtaccacaga acctgaaata aaagttaaa aataaatcat  
 31401 aaaataaaaat gttgaaatgc ctagaatgtt tcatacgatt aaattagacc  
 31451 atgcgtctt aatgcacatc ttatttcat agaaatcatg ttctgcttt  
 31501 ttctgtttt ctatgaaaat tttttaaca agcagaagtt aacgaaatgt  
 31551 atatttacc acttgggtca agaaacaaat gaaagtattt cccattaagg  
 31601 agcagttctt catactgtga taaatgaatg taagtattt gttacatag  
 31651 atgaagtata aagagaccaa ttaatgtaaa aagccaatac tgtacaaatt  
 31701 cctgaaggac cattattaa atctaacttt aatttttaga aagtcctt  
 31751 tcaagcaaac ttactgaga ccaactactaa ttatacttcc ctgctaaaag  
 31801 atacagataa tgacattgt taggccta aagtactact ccaatggaaat  
 31851 aaaatattta aatttgcac caagacccag tggtgctta tagagagtt  
 31901 ggtccaatat tcatggttct aatgtgatc aaaaagaagt cgttgttct  
 31951 ccttaattca acacccctca gaaaattggcc tattttaaa actattctt  
 32001 aagactactt ttccctccaag actctgccaa atgtctcccc ttggatcttcc  
 32051 caccataacc aacaaaaaca ttatttctc aaagttagaa acaaccctgt  
 32101 gtggccaaaaa tataatgtatc ccaacttcat tctcactctg gtttaagaa  
 32151 atgcgtgaat aattaattac tcatttgaa aaaaattaaag ctgtatccat  
 32201 atctatctta ccagattcca agataaactc caaataaattc aaagatttta  
 32251 attaaataag accataaaaat actggggcaga agaaatttggt aaactctt  
 32301 agaaccttgg aatctggaaa gattttctaa ttataactaa aaataaaaaa  
 32351 gtcataggag aaaatattga tagaataacat aaaatcaaag aataactgtat  
 32401 gataaaactaa acagcaacgt caaaagacaa atgtggaaaa atatttacaa  
 32451 ctcctactaa aaaatagaaaa ctaatcacct taaattataa ggagctctag  
 32501 aaatcaagaa aaacccaaca acctaacaga aaataaaatg gatataaca  
 32551 gactggtcac agaataagaa atacatatat acctcttaaa cataccagt  
 32601 ctcactcata aaaaagaat gcaaatgaaa gcattcttc acctatcaga  
 32651 ttggccaaaaa tctgcagttt gaccacacac ttatttgatg agactgcaag  
 32701 gaaataggca ctcacatgcc acaggagtgc aaagggttat caccctttag  
 32751 gaagagtgc aatattctacc aaaattactt aagcatttac tctttgaccc  
 32801 aggaagtcta cttectaata atttcatcaa ttgttagttaa atgttcacta  
 32851 tagctgaata aactattgtt aatccaaaca ataaaatataa gtggaaagacc  
 32901 tttctgcaca gctacagaag aatcccaaga tatgtgaaat aaaagaaaaa  
 32951 tgaatgtaa tactgcataat atgtgtgtt acctttgtgt aagaaaggag  
 33001 aaaaataaaaa gttgacttcc atattgttg tttttgtata aagaaacatt  
 33051 gaaataattt ttacaaaaag aagagaataa aatgtttaa ctgaggatag  
 33101 cgaatgagga cagcatgaat gggaaacgggt aggagtaaga ttttcagca  
 33151 tttacctttt tatgtcattt tgatgtttaa aatataaata tgtaactat  
 33201 tcaaaaaacta aattaaaaga attattgcct ggcacagatg aagtacagtt  
 33251 tagatgtga ctatttattt tttttgtatag caatatttgg atgggttaat  
 33301 gggctcatat tatgtcagtt tgttccgaat ctactcacac tccaggcact  
 33351 tttgtcatgg caaagagggaa caatgccaaa gataatttac cataggattt  
 33401 ccatgtgcac ctcctcagtt cttaggctgaa gtaacataga atggcatttt  
 33451 taactcacga aaaactctgt tctaaaagggt gctttattat ttgccttaat  
 33501 ttgccttca tatatttcc taattttaaa cttagaattt tagttgtac  
 33551 ttttcaaaagg attgcccag aagatgcaat gagatgatac atgtaaagt  
 33601 cttagcttaa tgcctgggtt ttaatcaata ctccataact ctttaggtt  
 33651 gcaaacagaa tcataaaaagt gatgtgtca gtgaaggccctc taatcaatcc  
 33701 tagaatcgat acctacaatc agaaaaaaat tatcaactca gaccatctt  
 33751 gtatgtttt gtttatttt ttctctcaaa atatcttcaaa taaggcattc  
 33801 ctagaatttg agagtctgt tatcttaaat aagaatgcat tttattttaa  
 33851 gaggttaatg gaaggagcaaa gaaccaagac aggtacttt tgagtctgg  
 33901 gtccttagat ataataagta atttcaggaa tggatgtat ggtaccta  
 33951 ggatgtgggtt taattagaag ggcttttggaa gctttcttgg agactgggtt

FIGURE 1L

34001 ttcattatgg cttcatctat gtttctccca gaaggcttcc ctggcctctt  
 34051 aactaagtta attgtccctg caatgtgc tc tttgttatttc ttctgtcata  
 34101 atattcatca ctcatgattt tggttactcg attcagcgtc ttctatgc  
 34151 accatgctt cagccttgc cagacagaag gcatccatct ggtccacacc  
 34201 agccatgccc tttaatatta tatgcccagg tcctagaagt ttctggccac  
 34251 aatgaatgt tattgaatga ataaaaattt gaaaaactg caagctgta  
 34301 aacagtca cagaagcgt catccccgg gccccatca caaccctac  
 34351 acacacaaag taaaaacaac acagtcaaca tgagcaataa gaaaaaaa  
 34401 atgtggcaat tattcaagca atgcaagggtt aaaaatagcc ctttgcctc  
 34451 agtattcaga gttttcaaa aggtatattt ttgcctgcat ttttaatct  
 34501 aatgtctca attatttat ttggcatgg gaacatgatt atattttta  
 34551 ataaaagtgc taatttgcattt gcatgtttt aattttagt tcttttacag  
 34601 gaggttgc tttttccata ttgcctttt ctcaattattt ttacttctgc  
 34651 cttttcaaa atgttttaaa tatttgattt tagccccatcc cacagactcc  
 34701 aaatctgtgc ttggaaattt gatcaaaag tactgttagt aatccctagg  
 34751 acatttgcctt ttgtgtact taagaatccca tctttatca agtttctgtg  
 34801 gttttcttgc gtttttacag gtcacaatgt caaaatgtgc acatctgaaa  
 34851 ctattttgcattt attatgtttt ctttataactt ttccatattt agttaatggg  
 34901 aaaaatataaa gtttttcaat ggtttagac ttcatgttccatccat  
 34951 cttttttttt aagatttca aagtttgc tttttttttt tcaataaaacc  
 35001 ttgtttttgtt tttttttttt aagtttgc tttttttttt aagtttcatg  
 35051 acatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35101 tttttttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35151 gttttttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35201 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35251 tttttttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35301 acatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35351 cttttttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35401 gttttttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35451 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35501 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35551 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35601 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 35651 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
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 36151 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 36201 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 36251 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 36301 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
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 36401 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
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 36551 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
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 36701 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
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 36801 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
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 37051 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt  
 37101 aatgtttttt aatgtttttt aatgtttttt aatgtttttt aatgtttttt

## FIGURE 1M

37151 tccccacagtc agtccttcag caagtcttgg cctctccacc ttcacaatgt  
 37201 gcacccaaatc cagtccttt acagcttc acgtactttaa cctcactt  
 37251 gtaatgctgc ttcacccctt tgtccagacc acagcagtgg cttcttac  
 37301 ggcctccag cttctctctt gacatctggc ttccttctg gcatccagcc  
 37351 tcttcctggt tggtttccca aaggtaccca aatgtatctt gtaaaataca  
 37401 catctgatcc tgcactctgc caaaaaccctt tccctgccc cttatcatata  
 37451 atacttagaa ggacatctaa agctattccc aaagctgtcg tgatctggct  
 37501 ggagccttctt ctcactccgc tcaagctaac ttgatctctt tgcctccct  
 37551 tgaacacactt gaacacactt ccaccccaag gtctttttat attttttgc  
 37601 ctggAACCAT ttttccttag atatgtatcac ggtcaccctt tcacttcgtt  
 37651 gggcatggc tcctctgaga tgcttccca ttgagacaac cgaaaataact  
 37701 aaaaacggcc gggctcgtg gtcacgcctt ataatcccg cactttggaa  
 37751 ggccaagggtg ggtggatcac ttgagtcag gagttcgaga ccagcctggc  
 37801 caacatggtg aaaccccatc tctccaaaaa atacaaaattt agcctggagt  
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 37951 gcaactccagc ctgggtgatc gagactgtctt caaaaataaaa ataaaaacta  
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 38251 aagctccatg agggcagaaa actcttctt ttttacttact gctctataacc  
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 38351 ctaatgaatg aataaataaaa ttgccttaac acttaattttt agaaaaagtca  
 38401 tatccaaaac actccttctt atgcttccctt gttcaaccag tatccaaaac  
 38451 aaaaatgtt ccaacttagaa ttgagaaaat tcaaaatgtt aaaggatcct  
 38501 tgagacttgc cagttcaatc caactatTTT aaaggatggg aaaccagccc  
 38551 tgagagataa gtgggtgacaa agctagttaa tggcgaacag ataattaaac  
 38601 taggcataatg tcaatgttctt ttatgttcc atgctttaca tctctgtt  
 38651 ttttggaaatg ttcttctgtat tacataagca aatataatgg aaccagaaca  
 38701 ctcttattcc ttcttattttt gctgtctgtt tggcaataaaa acatctggca  
 38751 catgatatac atgggacact aaaaaatattt taaatttctt cagaaaagggg  
 38801 ctcacattgtt taaggcagat tgaccccttctt gtcataatc gtcgtcccat  
 38851 tgggacaacc taaaatataaa aaaaatgtt aattataataa ttttactt  
 38901 attttacctg aatataactt atttgcacgtt agttatattt ctttatttt  
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 39301 cctgtggaaa aaaaatgtt atttccattt tggcggatgg gacttcaaga  
 39351 ctcagcaaga ttaataggcc caaggtcaca caactaagaa aggacagaac  
 39401 tagaaatacc tgggctgttgc ccatgttgc ttatatttcat aacccctgt  
 39451 cttcccttgc gggcttattt ggagaaacaa tggaaataaag tctgttact  
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 39551 atttcttcc ttcttccca ccactgacta aataaatttac cttggccat  
 39601 gtactaacct ttcttagggccca tagtttctt tttttttttt tttatgtt  
 39651 ctttttcttcc attacaaaatg caatacatgg ctattaaaga tcatttggac  
 39701 aaaaatataa tatataatataa taaaactaaa atttgcacgg aatcttacca  
 39751 ctttttttttccca ccactgacta aataaatttac cttggccat  
 39801 ttttttttttata tactataaga atacataatc tggccagggtt caatgactca  
 39851 cacctgtat cccagcactt taggaggccca aggctgggg atcacttgc  
 39901 gtcaggatgtt cgataccaggc tgcaccaaca tggtaaaaca tcgttctt  
 39951 tagaaataca aaaaatgtt gggcatgggg gcagggtccctt gtaatccag  
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 40151 agcaaaactg aatccctgtt atccctgtt gtaatcgtt atttttttt  
 40201 tgatgttttag aacattttta ttcacaataa ttcttctaaac acataatgtt  
 40251 ttgtggctgtt atccgttttgc tggtaataat aataatgtt aataatgtt

40301 tcaaatgtat gttagtattt tactgagatg tttcacagtt aacttattca  
 40351 attcttgcaa ccctatgaca taggtacctt tattatctac attttacaga  
 40401 taaagaaact gaggcacaga aagattcagt cacttaacaa ggtaaccagg  
 40451 ctattaagca gcagagccag gattgaaact gaggcacatg agcaccacag  
 40501 cccatgtct ggaagggata tagcatgtt ttttttatta atccatccctc  
 40551 attaaaatc tggtttttt ctcattttt atactgttac taatagtgtt  
 40601 aggtatgagc tgggaggaga aaaaaacaat agttaataa gtatgtgt  
 40651 gcaaacttgt taacatctac aattttatca tacatcccta cagtttaaat  
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 41201 gtttttaaga cctttaaaat tataacattt tatttttattt ctttccata  
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 41351 aaagcacccgc tgcatgcagt tgggttttta tagcttacta tagaagagac  
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 41601 aggtacgaga atttgatctt ttttttttttatttatttatttatttatttattt  
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 41701 aaagtggttt agagaaaaggaa aaaacaggag aatgggggggggggggggggggg  
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 42051 cacgaatata ggaataggca ataaaacata atagaatccc aaaataggct  
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 42151 atgggttt  
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 42501 aagtgttt  
 42551 tttccatt  
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 42751 taaataagggaaatgg  
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 43151 cagtt  
 43201 aggacttt  
 43251 aaaaatt  
 43301 cacaatgttt  
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FIGURE 10

43451 gagatcacat gacgagagat gaagcaagac ataagtgcc aaaaaaaa  
 43501 aacaacccaa tcttaaggga acttacagag ccagaactca gtcattactt  
 43551 caaggacggt accaagccat tcatgagcga tcctccccca tgacccaaac  
 43601 acctccatt agcttcacc tctaacaactg gggatcacat ticaacatga  
 43651 tatttggagg tcaaataatcc aaactatagc ataagtaatt ggtaattaa  
 43701 ataaattagt gtcctacctt atatacattt gtattgttt gatattttac  
 43751 tttataactt taaagtgtat attttattaa aattattcaa aacttagctt  
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 43851 gggaggggg gatataaaaca tcaagaacat tgatattgtc gtacttctga  
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 44001 tttacaaaaa tttaaaaagc ctgaagtctc cagacagttt ctagaagtca  
 44051 agatatacc tctttgtggc ttaatttactt cggaggggtt tatctgtcct  
 44101 tataactact agtttggaaat ttgtcaacca tgctttgtt gatccagatg  
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 44201 atacatgcattt tttgcattttt aatttgcattt acaaaaacaca gtccatcagg  
 44251 ttcatgttta caatttggctt tgctcttacc caatccttga gttcacaata  
 44301 gggaaagctt ggtatgtaaat aatgaaggct ttttggattt tcagtgacta  
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 44401 ctaaataata ctttgcattt gttccatgtt catctaaaaa taagctctt  
 44451 cacagtcattt atgtgtcttta aatatcattt tggattttt tttgttcaaa  
 44501 tctttgcattt cacctcaaat ttcaagaattt catgtgtaaa tcatttcaag  
 44551 tgatgcattt aatttgcattt ccttacttcc aataccattt aaacccatata  
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 44851 ctccctgcac ttttcttgc tcttgcatttgc ttatgcattt acaatttattt  
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 44951 tccatcccttca tcccaacccttgc gatggatgg tataccataa ttcttaagga  
 45001 cacagcttttgc ggttgcatttgc agggccatgtt caaccacttgc tgcatgtttag  
 45051 tgacttgcatttgc actatgcatttgc tcaatttgcattt cattttataag aaagagaagg  
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 46501 ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc  
 46551 ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc

FIGURE 1P

**Exon 4(A)**

### Exon 5(B)



## FIGURE 1R

52901 aatgaaaagca cctttaatac aaaaggaaca aaaaaagagt tatgtgttt  
 52951 gatgcagacc cacagttga acacagaaga ggcttggaa ttggaggtg  
 53001 tggatgaaaat atgtcctggg ttctgtatgtg gcaactaaag ttgcattgt  
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 53101 tgctggaaaa gggatcttc tgatgttgg atagagctcc atttattatc  
 53151 attttctatt gtatgttgc tcatttttgg ttgttccaga tttatttctga  
 53201 aataattaa gaatgggtt ccctggaggat attttctgtt attaaatcct  
 53251 tcctgttttgg tggaggtgtat ttttctctt ttgtatgtctt ttagatttat  
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 53351 agtgagaccc tgccctcaaag actcccttgg ggagaattat accgtgccac  
 53401 ggaaatctac caacagtata ttgttccaccc gaacacatata gctataaaact  
 53451 aatgtacata gatttactaa aaacataatt gtatcttcaa aatcaggtca  
 53501 ataaatattt gttgatttgt tgccctgaaag aaagaaggat ttatatctcc  
 53551 tgatttggaa ttaattctgc tattgaaaag aaaaaaaact ttagcttaac  
 53601 cagtgcttta aattataatc tgaccatagc ctcagccatc tcattaaaa  
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 54501 aaatatttgc ttgtttttttt aatagagtag aagctctcag aacttattt  
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 56751 gctactcaat tcatgtacaa aggatcaat gataaaccatt agcaggggct  
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 59051 gagaaaaggg ggtgaatttgc caaaaaccta aggagatcga atcaacagga  
 59101 cttgctgata gattccgtgg ggggagtgag ggaatgaat agttaggatg  
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## FIGURE 1T

59201 ttaagacagg aaggaatata tttggtaga ataagagttc tgaaaaatgg  
 59251 acattaagtt aaatgactgt gacatctaaa tggaaactgtc aactgcagat  
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 59351 gagtgtttag cataaaagtgc cattttaaat ctatgagaac atttaagatc  
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FIGURE 1U

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FIGURE 1W

## FIGURE 1X

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## FIGURE 1Y

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75651 gtgactatag ttagtaataa tttattgtc cattttaaa taattaaagag  
75701 tataattggc ttatgttca cacaaggat aaatgttgc ggtgtatggat  
75751 accttttta ccctgtatc atcattacat atcgatgc agtataaaaa  
75801 tatccacat aactcataaa tatataaac tactgtgtc ccacaaaaat  
75851 taaaaattat taataaaattt ttagttgtat tttttttttt caaggatgtc  
75901 cacttttgc acttctattt aatatagttag tggaaatgttca tgccagagca  
75951 gttagacaag agaaagaaaat aaaaggcatc caaataagaa aggaagaaag  
76001 gaaatttttgc ctgtttgtc acaacataat cttatataa gaaaacccta  
76051 aagattccag aaaaaactg ctagaactaa taaattcagt acagttacag  
76101 gagacacaat caacaccaca aaaatcacta gcatttctat acactaaca  
76151 caaactttcc aaaaaagaaa tcaagagagc aatcccattt acagtagcta  
76201 caaaaattta aataacttagg aataaattta accaaggagc tgaaagacct  
76251 gtacacagta gtctataaaa tttttttttt tttttttttt tttttttttt  
76301 atcctttta aatccacccat gccccagttc agctgaacaa ctcataacttt  
76351 tcagaatcta ctctatgtt tctactgtt ctgcagctag ccaccccttt  
76401 ctccctccca gatcacccctc tttttttttt tttttttttt tttttttttt  
76451 cctctttcaaa agccccaggta tgatgacatc tcccttagtaa agctccctca  
76501 acaccctcaag cttataataa ctaatctttt cttgttattt ccatagcagg  
76551 ttatgttgc tttttttttt tttttttttt tttttttttt tttttttttt  
76601 ttatctatgt gtggcatgtt tttttttttt tttttttttt tttttttttt  
76651 aagaactatg cccttcattttt tttttttttt tttttttttt tttttttttt  
76701 gcacacacca gacccctcagg aaatgttgc taaggttacg aaggagacagc  
76751 ctaaattaaac ataaattttt tttttttttt tttttttttt tttttttttt  
76801 ggtgtatc tttttttttt tttttttttt tttttttttt tttttttttt  
76851 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
76901 acaagttatgt aggttattttt tttttttttt tttttttttt tttttttttt  
76951 cgtcacggaa aattttttttt tttttttttt tttttttttt tttttttttt  
77001 gaataatgtat tttttttttt tttttttttt tttttttttt tttttttttt  
77051 cttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
77101 TTACATTGAC AACTATTGGC TATGGAGACA AAACCTCCCCCT AACTGGCTG  
77151 GGAAGATTGC TTTCTGCAGG CTTTGCACTC CTTGGCATTT CTTTCTTTGC  
77201 ACTTCCCTGCC gtggatgtt tttttttttt tttttttttt tttttttttt  
77251 ttagagactt attagagtga gctctcacaa attcgttatgc ttggggacat  
77301 atctatataca ttacaaata taatttttcc gatataatgt tgactttttt  
77351 aaatataatct acttggataa tttttttttt tttttttttt tttttttttt  
77401 cttatctga gactttttt tttttttttt tttttttttt tttttttttt  
77451 tcatttcagat ggcttcattt tttttttttt tttttttttt tttttttttt  
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77751 aagcttcattt tttttttttt tttttttttt tttttttttt tttttttttt  
77801 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
77851 cccccatttt tttttttttt tttttttttt tttttttttt tttttttttt  
77901 gaggagccaa tttttttttt tttttttttt tttttttttt tttttttttt  
77951 gggaaataga tttttttttt tttttttttt tttttttttt tttttttttt  
78001 gagaccccttc tttttttttt tttttttttt tttttttttt tttttttttt  
78051 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt

### Exon 6(E)

78101 ttgagattca ccagatcggtt ctgccccaga acactaaaa tcacagaaaa  
 78151 gagactgaaa agggcatgca tatgcttggg tactagacct cagtttgaat  
 78201 acatcttgc cacatactaa ctatatgact gctttagttt actagggtcg  
 78251 ccttaacaag taccacagac tgggtgactt aaacaataga aaggatattgt  
 78301 ctcacagttc ccaagactgg acgtccaaaa tcaaaagcatt gagaaccac  
 78351 gagagccatg agagaaagaa ctgttccagg cctctttct tggcttata  
 78401 atggctcttc ttcctgtgtc ttcacatcat ctgtgtccaa atttctactt  
 78451 cctagaagaa caccagtcat atttgattag gttccatctt aatgacctcg  
 78501 ttttaacttg attacctctg taaggaccctt atttcaaaac aaggtcacat  
 78551 tctgagggtca tggggattag gacttcaaca tatgaattttt ggaaggacgc  
 78601 aattcagcct gaacagtgcac cctgaataag tttctttttt aatagaatgg  
 78651 aggaagaattt attgagccca gagaattttt gtgcggacca atgtaataat  
 78701 gtaagtcaag tgcttgcattt gaagagaact ctaaataaaat gttacttccc  
 78751 tttgcgtgtca tgaatctaga aatacatgtt tcctggacca aaacgtgaa  
 78801 atccagggaga attaaaaaaa aaaaatcttac gtatccaagg caacttcattc  
 78851 tggcaatctc aacaatttcag aacagagaag agattcactc aataatcaga  
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 79001 tcctgaggcc acatgttagag caaccttacat gattcgtga aaaaactatga  
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 79101 tctgtcctca taggagagcc acttgagacc taattcataa cctagtcttc  
 79151 attcagagaa aattctgata aactcaccta tatggtttca caattcttg  
 79201 aagattataa acaataaaata tagaggaaga tgatagaaca aacactgcaa  
 79251 cagaaagaaa tggtaaaaga ctaacagcaa aagaaggaaaa aggaatctg  
 79301 tgagtgcac gcaagacatca atgttcaaaa tgggtatctt gtcagtaaaa  
 79351 ataaaattaa attaaaagggg aaaaacaaaat gtatgaagat cttagggccaa  
 79401 ttagtggtag ggtcaacaaa cctcttgcac tggctgcac ccagcacagc  
 79451 aaaaaggcag tccccataat gaaactctaa actatcacag ggaggtaaa  
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 79551 aatgtttcca ataaaagtaag tatgaaattt ttatgtcaa attaaaattaa  
 79601 cctatgttgg aaatctgaaa attttgtttt cacagaaaaat tacatttctt  
 79651 aagaacccca agaaaaagtaa cctctactaa ggatctttt ctgaaacttc  
 79701 acaatattttt ctgagtccctt atttattaaa tgaagactg aatggtccat  
 79751 atataccctt agaaaaaaac aagatttgcac gatattttat tatatctgt  
 79801 gtatctgcac accaaaagag ttgtctgatt gaaatttttagg aagacacatt  
 79851 gacattttgc tgagaaagttt agagggttgc tggggctgc ccctatgttag  
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 80251 aactgtgct gtttgcactca agatattaac cattccattt aaaaatttgg  
 80301 ccactgtaat ccttaacaat attaactaaa tgaatttattt gcatataata  
 80351 acatgttaaa aaccgtttaa aaaaacaggg catcttgcgt ggcgtgtga  
 80401 ttcacqccctg taatcccacg actttggaa gccgaggcgg tggatccaca  
 80451 aggtgaggag atcgagacca tcctgcctaa catggtgaaa ccatgtatct  
 80501 actaaaaat aaaaaaaatc agccaggcat ggtggccggc acctgtatc  
 80551 ccagctactc gggaggctga ggcaggagaa tggatgtaaac ccaggaggcg  
 80601 gaacttgcag tgagccgaga tcgctccact gcaactccagc ctgggcaaca  
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 80701 tttcagatttgc gcttatttgc tatgttggg ttacaaattt ggttcat  
 80751 atccagaaga taatgaaggg taaaattttt tacattttt ggtgtc  
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 80851 tatataaaaa tataatagac cttatttca cagacttctg tttaggtca  
 80901 ccaagctgtg tactaagaga gaggtggaaa aaaaattggaa aggacccat  
 80951 atgagacaat aaggcagaccc ggtttataa ctgctgtat gtacagtctg  
 81001 ggcgaagaaa tacgttagtga acatttacca ttcaactata tatgttacc  
 81051 agcaatgcacca atgtgatttt cagcacattt tagattttt ggcagatgt  
 81101 aaatttgc tatgttagggc ctgtctttt ttccaaagg ggattaaact  
 81151 ccgaacctca catccacatc ataagtgcctt aaaaatggtag ctgtgt  
 81201 taattcaatg tctgcataat ctaaattatg ctccatacaa gtggattata

81251 cacatatatg cacataaatg catgtatata tactacatat tataaatata  
 81301 tgccagaaaat ttggattt catattctt tacatgtcta cacttatga  
 81351 aaagtagtat taaaggaaa ataaagaat ctttcctaaa tgatctaca  
 81401 cagcagaaaa aaattagaag ttacaaatga ctaagtgt tctggattt  
 81451 gaaatggagg ggcattttt taacaccaa atgggggaa atgttggat  
 81501 aatctataaa ccagatcaca gagaccagg tttataaag cttagttgt  
 81551 acaatcacaa cctgtatgag atagagatct tagacagcgt aagacagtca  
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 81701 gtagcaataa gtattatcg accactgcat attttaaaca tgattgcatt  
 81751 acttattgtc tggttattgt cactgtatc ctcagaatgt tggaaatctca  
 81801 agataagaag gaaggtaaa ggttatctag agcccaaaaa tatctcagcc  
 81851 aagttttat tcagttgaga cttaacacct tctagaaatg aaaaacccac  
 81901 cacctccca gacagccat agcatctt aaccatctt gagctactct  
 81951 aaaaataaaa agaaaagaaa agcaaccatt ccttacctgt agcaaatact  
 82001 gacttagtgc ttataaaatg tccatctcta acgaaagggt tagactcctt  
 82051 gaagtttaat aaaaaactaa taatttatacg ctgcaagta aaatccacag  
 82101 acttggaaagc agcagagctc ccagccccat gctaataaac tcaagatgtt  
 82151 aagacaaagc ccagagactg aatttacaa gtcacaaaag ccaacccaag  
 82201 gctgagacaa agcatcttgc ttttacaaat gtagtagac cagagcaat  
 82251 taaaaagagt gggggacatc aaagaaccag aattttggca gatcaagatg  
 82301 ataagcagaa gaaaagcaaa ctggccaaa actaatgtaa acctagaagg  
 82351 gaatactaattt ctactaattc cccaaaactg aataggtgag cccaaaataaa  
 82401 aaaggcagg aatggtaaaa gtgtgaatta aaatggaaat gtgcttgca  
 82451 atgatccacg ttcttgc ttagtgcataa atggccaaaa tagaaaaaccc  
 82501 tctactctgt atcttcaaaa ctgagtatcc ctgctctcca ttttactttt  
 82551 ctttttagtag gtgtacgtt ataaacattt aaagaactac agctggaca  
 82601 gattttatac agtccctctt cctccatcc atgaatagag aatctaactt  
 82651 tcagagtctc atcaaaatgc tagaagtatt cccatgttca cagcagttag  
 82701 actttaactc cctcagattt aaaaatccgc tctgtcccaa gttgaaattc  
 82751 atgttctcta cattccatca ctggatgaga cccatcaatc taacttaggc  
 82801 aaaaagaaaat gtcacagaga aggccacaca cacaaaaaaaa aattttattt  
 82851 tgattttattt tataatcatg gtgcctatgc tataccacaa aagataataa  
 82901 atgacaatgc ctaatttgact tactaaagaa cagaagttgt atctcctggc  
 82951 agtattggcc aacaatttgc cattggctat tggtattata atggagataa  
 83001 atactgctta ttttataaag taacatgttt atggacaggt tacataaccgt  
 83051 ttgtcttctc tcagactcat tttagtgcact ttttataattt ttttattttt  
 83101 aacagtgcctt tgaaatttt tgagtccat ttttgcattt ttttccagGG  
 83151 CATTCTTGGC TCAGGTTTTG CATTAAAGT ACAAGAACAA CACCGCCAGA  
 83201 AACACTTTGA GAAAAGAAGG AACCCAGCTG CCAACCTCAT TCAGgttaat

Exon 7(C)

83251 gtcaatgttaa taggttagatg gcaacatttgc tgccatagt gttgtatgg  
 83301 tcattttccaa atctctgtgc ttcatgttgc ggttagaacta ctgctttgtt  
 83351 ccttttcata aaatgaagtc agaacttaat gtacagtctt ggattttggac  
 83401 agtcttggat ttgttcttgc tctcccaac tggaaacacat gtatttttag  
 83451 caaatggtcc atgcattgtt cagactaagt aaccatgtca gcaaggccat  
 83501 gcaaagggtt gcaatgttgc ggctcggtt attatctaat atgtcttatg  
 83551 aattacttgc tggaaacgttgc ttgtatcattt agtgcatttgc ttttgcattt  
 83601 cattgttccc tgcattccaa ttacttgc tggatgttgc ttttgcattt  
 83651 ttttaaagaa caacatattt gtttgcatttgc ttttgcatttgc ttttgcattt  
 83701 aattgcattttt agtgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 83751 ttgagagctg atggactat ttttgcatttgc ttttgcatttgc ttttgcattt  
 83801 aataagtata taatttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 83851 tatttcattt ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 83901 atgcttctcc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 83951 gaatcacaatc atatattttt ttttgcatttgc ttttgcatttgc ttttgcattt  
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 84051 ggaagtggaa gtttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 84101 ccaaggccctt agggaaacttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 84151 ttgttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 84201 ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 84251 atctcggttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 84301 ctcagccctcc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt  
 84351 taatttttttgc ttttgcatttgc ttttgcatttgc ttttgcatttgc ttttgcattt

FIGURE 1AB

84401 tggtctccat ctctcaaccc tctgtatccgc ccaccccggt ctcccaaagt  
 84451 gctgggatta caggcatgag ccacggctcc cggccacaag cacaactgttt  
 84501 taattttagat tggtaggtttg ggtgggtggg ttgggtgggag ataaccacca  
 84551 caacccctac ctttagtgtt gatctgtac tggatataat gcagtgcctc  
 84601 ccacagacat ggagctgggg aaagaagggg gcagatgtt tcagttat  
 84651 catgaaggag atctgtttat atctaatcat taaaatggga tattaat  
 84701 taaaatcaagc tattctt:aa ctgttgacaa gaaaatgtac catcaggcat  
 84751 gacttccagt gcaat:act gagaatctct atttttttac attttttt  
 84801 acaatttttt ttttttacat attcttaca ggttttaaaa ggtcaactaaa  
 84851 gagaaggtaa actctatttt cttatatgaa gttggagttt aagatctgat  
 84901 gccaaacaat aatcagcaga atgaaaagag gaggcacaca ctttagaca  
 84951 cacgcaaaaat accccaagg ccagaattca taggcttca tcctttagca  
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 85501 aataattttc aatttgaactt gaaaataaaat tggatatttct acagcaatc  
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 85751 gtttttattt tactttaaaac tccaaactt aatgttgcctt taacaaaaat  
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 85951 tattttttt ttcattttt ttcatttttca tagtctttttag acagaattca  
 86001 aggctttttaag ctttgattat atattataga aattttatatt tcaggatgt  
 86051 atagatttggaa aagcaaaactt cattttatca tcccttcacc ttcttaccca  
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 86151 ttcattttt tttaggccag agtcaactgtc ttctttaaaag ggcaactgag  
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 86251 catttcaggg ttttagggaa aaaaattttaaa accccagaag ctgcagcaa  
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 86851 aataaaaaac agtgcagggt gtttttttttcaatggccac tagtcaattaa  
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 87251 ggacaggagt ggcacacgtt gaaacttagaa taaacagaga  
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 87351 caaaaaggggc ttcttcaatggccac tagtcaattaa  
 87401 gaataaggat gacataggat ttcttcaatggccac tagtcaattaa  
 87451 aatgaaaacaa tacttttccaa attatccat gaaacttagaa taaacagaga  
 87501 tataatccacgc caaaccacca tcaatggccac tagtcaattaa

## FIGURE 1AC

87551 taggcattgca agatctcaaa aattaatcta ccatttaccc ttactcaaga  
 87601 aactttgtaa atagaacttc tcttccacaa caaggggata agccaagaga  
 87651 gaaagagaca tggagtcaag aaaacaagag atccgcaca ggaaagagca  
 87701 aaggggattt ctatgataat agggaaaggga agtcccaaga caacagctat  
 87751 gcaggccctg agaacagaat gagaaggagg ctgagagctc caggagaaag  
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 88051 taacttagct aagaatttgg atattaaaat gttgatagga tgaaaggagg  
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 88201 aatccttaaa aataagcatt cttggcttgc cgcaggatggc tcattgcctgt  
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 88501 agtatgaccc ttgtctaaaataa taataaataa ggattcttaa  
 88551 aaatagaagc aacaactata agaatttgaag gggttgcctc tgaggaaacag  
 88601 aaagtatgtt gaagaaagat gtggaaagggtt atgtctgggtt catagcctaa  
 88651 aactttcagg accttcacat tttaaactt gtaatcatttggaa aaaataagct  
 88701 ctgtgttcat tattttttt gatgggtcagg tggaaacgttc taaaccatcc  
 88751 ccagtaagga tcaaaacatgc cataatggta atacttgc gacaaacaaa  
 88801 atactcccaaaa aaaaacttggaa ttatacttgc ctgttacttta ttgagcaaaag  
 88851 tccaaatctc ttgtacttgc tagagcacca gcatcaccctg ataaatggca  
 88901 aagttggctc tcaatgttgc tttttttt gatgggttgc aatttttttgc  
 88951 accatgtaaa ttaaccatag gaaatccctc taatgtttt ttttttttgc  
 89001 ccaactactg ttgttccat gcttttataa taggaacatc agctacttgg  
 89051 tcacaggat gtgggttcaaa agttcagctt ctagaaacaa tttgtcttgc  
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 89151 cactttccac ctttcattttt actgtttaactt aatatcagcc atgtgcacaga  
 89201 tgccacccgc accttcataa ccttcattttt aaaaaggcattt ttttttttgc  
 89251 gagtaatggaa gggaaacaaga gcttagtgc tggatcaat ctgagagaaaa  
 89301 aatagaaga catcagggtt cattttttt aaaaatcttta attttttgc  
 89351 agtggccctct tttttttttt gtttgcattt acatttcacag gcaatgcctt  
 89401 ggtcccatc ttttttttgc ttgttgc ttttttttgc actggatct  
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 89551 aataggc ggcgttgc ttttttttgc ttttttttgc  
 89601 cactactaca gaagaagctg caatctttaa ttttttttgc  
 89651 attctttaatc actctttaaa ttttttttgc ttttttttgc  
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 90151 catggatgttcc atccatgttgc ttttttttgc ttttttttgc  
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 90251 ttttttttgc ttttttttgc ttttttttgc ttttttttgc  
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 90351 ctttttttgc ttttttttgc ttttttttgc ttttttttgc  
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 90451 agcatacat ttttttttgc ttttttttgc ttttttttgc  
 90501 acatttttttgc ttttttttgc ttttttttgc ttttttttgc  
 90551 agggatgttgc cccat ttttttgc ttttttttgc ttttttttgc  
 90601 gctgttcat ttttttttgc ttttttttgc ttttttttgc  
 90651 gaggagttca agatcagcc ttttttttgc ttttttttgc

FIGURE 1AD

90701 aaaataaaaa aattagctgg atgtgggtgt gcgtgtctgt agtcccagct  
 90751 actcaggagg ctgaggcactg agcatcgctt gaacccagaa ggcagaggtg  
 90801 gcagacagcc aagattgtgc cactgcactc cagcctgggg gacagagggaa  
 90851 gaccctgtct caaataaaata aataataat aataataggttt gtcacataaaa  
 90901 ataaaaatgtt ttgattaatc tactataata aaaaagttt ctctgagggg  
 90951 actggagtaa atacctggcc attagagatg tttgcagact cattaaaaag  
 91001 aaagaaaattt accaaaaatct atatggaaa gtaaggctgg gcaatcttc  
 91051 aaatgagcag ttcagatgga agctttcca ataacagtct tcaaggagtc  
 91101 agcaagtctc cgtggaggga ttctatgact gacagccagg caatctgaga  
 91151 tattgtctca actccacca ctttgtataa acctcttcat ttatctgagc  
 91201 ccttttttcc tcacctacaa azzggaaatc ttaattcaca ctttgcattgt  
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 91301 gaaatggaga gaggatgtt ttacatcaa agactataa acatatttt  
 91351 agatcatggc ataataatcggt aggtgtttt cagttatcata cctagagagt  
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 91451 ttttagcat tagaagtatt acatagttca aggatttcat taatttcaatc  
 91501 actagcatac cctgggttcc attagttaa tagttatctt actatgtca  
 91551 taatggattt tcattatgtcc ttgccttctt ccttataaaa tattgattaa  
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 91751 ttttgggcct tttgtttttt ggtatgtt gttaaaaga agtctgtgg  
 91801 aggcacagtg gttcataccct gtaatcccag cactttggg ggc当地aggca  
 91851 ggc当地gatcac ttgaggctcg gaatttgaga ccagcctggc cagcatgtg  
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 92101 aataaaaataa aataaaaataa aagaagtctt gatgtgggtgc aatatgttta  
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 92201 tcagggtcaa gtataagagg caaaagatc ttatgtgtc gtaacttaat  
 92251 cattttctt tttatctt tctaaatctt gctctttttt ttcttttca  
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 92351 TGAGAAAATCT GTTTCCATTG CAACCTGGAA GCCACACTTG AAGGCCTTGC  
 92401 ACACCTGCAG CCCTACCAAAG taggtatcag tggtacagct gcaactgttag  
 92451 ttgagtcattt tcaagtctgt taaacaaaaacc atacccacac acacaaaaaaa  
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 92551 aaacctattt agtagcagtt ctggcacaaaa actaaatggg atcgtatca  
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 92751 aggattattt attttgcacc catgcctga ccccaagaga tgactgctt  
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 92951 acaatgaggc aatgggaccc agcggattaa aatttggat ttgcattcac  
 93001 aattttaaag taagactact ttcttccata ttcttgc当地 caaatgtt  
 93051 cactcagcca tgc当地aaattt caaagaaaaat ggggaaatc aattttac  
 93101 ttttccatgtt gctttagaagc aggcaagaac caaggacatt atggacagtc  
 93151 ctaatgatta cc当地agatctt ctgtatcata aaaaaaaaaa aagggcttag  
 93201 tcttggagtc ttggaaaacctt ggactccagt tcaactatca cagaaaatgt  
 93251 taaatcatat tcaccaccta attaaagaag tc当地atc当地 aataccgaag  
 93301 cagtaagtca tgagaaaaggc ttctgtgg tc当地ccagct tgattagcgt  
 93351 agtcaggatcc tcaggatgtt caaaagttt taaatgtctc atccgacatt  
 93401 tgagagcacc agtc当地ttt cttcatagcc caacaaaacc ttaatccttag  
 93451 tggcttc当地tgg gggatcacta ctgtgactca caaaaaaaa  
 93501 cctgttc当地tgg ctgatcttgg gagatatcag ctggaggaaac ctccatgaca  
 93551 ttccctggca gtaccgtctt aatggagggtt tggatgc当地 cagaatgc当地  
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 93651 gccc当地ggcc tcagtttcc caccatcataa gagaaggaca agatgtgg  
 93701 aagatgatcc ttaagctctt atggaaaatg ccttgc当地 ggtggatct  
 93751 aaaattcttgc tcagcacatc ggacagagat attcatagca ctccaggat  
 93801 ttcagagagg atggaaacctt agcatggata gaagcatggta tgctgtt  
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Exon 8

FIGURE 1AE

93851 tgcatgtttg gattaaaatc ctctttcat ttagatcttg aagtttagtt  
 93901 gaactttta tggagttaa gacccttca acattttat atcaaaaaac  
 93951 cgaaaataga acctaactcc tggccattt attccttggg agtatgaacc  
 94001 aaaaataaaa attatataga aattgtatcc tttgtttca tgaagtttgc  
 94051 taggttaatg taaaaggaa atctgatgt gaaaactgtat agagaattct  
 94101 caagtgcac aggagatgg tctattatca tatgtgatcc tttggcttcc  
 94151 cacttactgc agtttttgg taaaaggaa taaaaggctt ggaaaaactg  
 94201 tttataatg agtcaatcc ccccaatgtt tcaactatcc ttttatttcc  
 94251 ataaggttt tctacttcc tttatgtt cctgtttaa gtgggggtgg  
 94301 aggtgggaa ggatgttgc aaacacccgtt gtcttcatgtt ccctactgt  
 94351 cctttccctc actttccctt tcctgcaaac tcatgttcc tggggctcag  
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 94451 gttaaaggcc atggggaaat agatgttcc ttttttttca ctttccatgt  
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 94551 ttgttaacc attgagaatg ttttttttca ttttttttca ttgtatgttt  
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 94751 acattttattt gtttttttca ttttttttca ttttttttca ttttttttca  
 94801 caatttttattt ttttttttca ttttttttca ttttttttca ttttttttca  
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 95351 ccaggatattt ttttttttca ttttttttca ttttttttca ttttttttca  
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 95651 taaaggccattt ttttttttca ttttttttca ttttttttca ttttttttca  
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 95751 ccatgggtttt ttttttttca ttttttttca ttttttttca ttttttttca  
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 95851 tactccaaat ttttttttca ttttttttca ttttttttca ttttttttca  
 95901 gcaagtgtact ttttttttca ttttttttca ttttttttca ttttttttca  
 95951 gtctgccttgc ttttttttca ttttttttca ttttttttca ttttttttca  
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 96351 GCAGgtttgtt ttttttttca ttttttttca ttttttttca ttttttttca  
 96401 ctaccaggat ttttttttca ttttttttca ttttttttca ttttttttca  
 96451 acaagatgtat ttttttttca ttttttttca ttttttttca ttttttttca  
 96501 ttttttttca ttttttttca ttttttttca ttttttttca ttttttttca  
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 96651 agtcttgc ttttttttca ttttttttca ttttttttca ttttttttca  
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 96851 tatacatata ttttttttca ttttttttca ttttttttca ttttttttca  
 96901 atataatctt ttttttttca ttttttttca ttttttttca ttttttttca  
 96951 cagatcttgc ttttttttca ttttttttca ttttttttca ttttttttca

Exon 9

## FIGURE 1AF

97001 ccccatcccc atcttttagg aagaagacaa ccctcccaa aattcccaa  
 97051 ataatttattt atcagcttcc catgacttag atgaaatgcg tcgtcagatt  
 97101 acagcagaga attaaaccta gaggaaatac gaggtgaaag aaaaatttt  
 97151 ttagatctgtgt taatgagtag caggaagtgc ctagatttga gagcaaagcc  
 97201 ctgaaaaaca gagccagggtg gaacccagta ttaatgatgt gaagagtggc  
 97251 agaggcagaa ccagcaaggga gaatcccagg tgctctggaaa ggaagaagag  
 97301 atacattttt ttctctatca ttgtcactgt gttccataa agaaatgaag  
 97351 gcatccaccc acccagagtt ggtccctaag tggaggccag tggggccca  
 97401 gggattttc ttttagctt gtactattat aataattata ttaataataa  
 97451 tatattttatg caatactgaa gccagtttggaa aggttcaact tgggttattt  
 97501 aggctcttgc ttatccattt ttgcattatg tttatatgtt aagataaaca  
 97551 aatgaaaaaca taaatgcatt cgtctatgtt gggagatagg cacgatagg  
 97601 tataacaacat caggcacatc ttctgcgttag gtaacctacc caagggatgg  
 97651 cattaaagtt cttctcttta ttggtagca tagatgtt gccaaggggca  
 97701 ttggatattc ttggagata ttccagaaa aaagtcatc ttccccaccc  
 97751 aagaaacgtt ttggacaaa gagaggttct agtcatttga ttggaaatag  
 97801 tctttgccta gacactggaa gagacaagct gaccaatttct agacttttag  
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 98301 cttctgtca ctatccaaa aacaagcttc ctattcagtt atcactattc  
 98351 aaaaaaaacta ccaacccaaa ttccacattt tatgtgttc gcatatatct  
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 99951 agagttttt aatataatgttgc caactgatgttgc atgcttgc  
 100001 tcagttttt ttgttgcatttgc ttcatttgc atgcttgc  
 100051 gcctgcgtt ttttgcatttgc ttcatttgc gtcatttgc  
 100101 ttatcttgcatttgc ttcatttgc gtcatttgc

FIGURE 1AG

FIGURE 1AH

### Exon 10

## FIGURE 1AI

106451 agggatatct cttccacgct caagtgagca acacaagtca cctttcacg  
 106501 cctcactcca caccctgtg ggtgcacatgc tcttcagggc gaccctagt  
 106551 ggctgcactg acgtggctcc tccctggcgg a gttgcagggt cccatatggg  
 106601 cgcaagacgg ctgatccctgc catgttccc cgcagcctgt cctgtgtaa  
 106651 ggaggaaaa acctccgcca ccaacacggg acactccctcc atcgagccac  
 106701 ttgcaggatc ttagtcaattt gttggcacage ttttcagtgt cctctagtt  
 106751 cctcactctc ctccctaggat tttggctgaa agcccttgag cagctgagtc  
 106801 aagagttacc agtgacaggg ctttatgtt cactaaaaat aggcttgctg  
 106851 aatataatg ggtacatcct ttctggaggg caatttggca aaatataat  
 106901 aaagtcttta catatgtctca agcctagaca catcccaccc accaatttta  
 106951 tttcttaggtt ataatagaa caatgaaaca atgtcaggca ttagaaatga  
 107001 tgctctaaat taaaatttt tgacacagaa agatgataac aaaaaaatca  
 107051 ttccattttt atatattata taaaatttcatg tatctataagg aacaagtctg  
 107101 gaaagatata caagaatgtt tgaacagttt cttttgagtg gtgagatcac  
 107151 agttatattt ttttttttca ttttttattt tttttttttt aatatttctt  
 107201 caatgaacag gtaa gtttct tttttttttt aatatttctt  
 107251 tttttttttt aaaaagcc tttttttttt aaaaacaaaaat gtttaggggaa  
 107301 aaaaaagaaaa aaaaaaaacta gccccttcaag aaaaaaaaattt agcccttctt  
 107351 ttcacacact gccccttccctt cttttttttt aatatttctt  
 107401 ctgttactca cctaacaccc tttttttttt aatatttctt  
 107451 gaaggagcag ctgttctttaa tgggtggaaac cagtctttt tttttttttt  
 107501 catagactat gtaatgtatgt ttaatagctt ctactacaaa tggaaacttgg  
 107551 attagtttgc tcaagctgtt ataaacaaatg actagatgcc tttttttttt  
 107601 aaaaattttt ttctcacatgtt ctagaggcttca gaaaggccaaatg tttttttttt  
 107651 cagcagggtt gttttttttt tttttttttt tttttttttt tagatgtct  
 107701 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 107751 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 107801 ataaacctcat tttttttttt tttttttttt tttttttttt tttttttttt  
 107851 gtcgcattcg gaggacttag gggtttaggac cttttttttt tttttttttt  
 107901 gggatgtcaat tttttttttt tttttttttt tttttttttt tttttttttt  
 107951 atccctggaa agtctttttt tttttttttt tttttttttt tttttttttt  
 108001 cacactgcattttttt tttttttttt tttttttttt tttttttttt  
 108051 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108101 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108151 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108201 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108251 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
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 108351 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108401 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108451 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108501 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108551 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108601 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108651 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108701 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108751 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108801 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108851 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108901 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 108951 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109001 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109051 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109101 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109151 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109201 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109251 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
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 109351 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
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 109451 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109501 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt  
 109551 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt

FIGURE 1AJ

109601 ataaggtaaaag gagccaccat gcacatgcag gcaattgaat ttacacgggt  
109651 tccttacaaaac gtattctaaag atgttcttcc agatattata tcaatttccc  
109701 tttttaagaatc ttttcatttct tccccctcccc caaccccccac caccctcttc  
109751 ttgcggctgctc tcttccaact tcaatcggtc agattccccct tccccatataa  
109801 gccacttgac catgaccatg ccactatccc atctttctcc cagcctcagc  
109851 tgccaaacacct ctcaactaca tcatctcaag gcagccagag ctagaagatt  
109901 aggcaaaatttgg gggaaatggc ctttcaatga ccgttctctg ttttgcataa  
109951 gtatctggga agagactcag gataacagcc atactggctc gtgtctatTTT  
110001 tccccctggagg gaggccaaatg gtagggtcat ctgaggcctg tttcaagatg  
110051 caaaaagatag tgcacagaaga tgcacaggtg tggcaacag acaagcaagt  
110101 ggaagggtggc agattgcag cgagaaatgg agcaagcgc caaaatccac  
110151 aagaatgata ctaaggtaga gctaggagaa aatcttcgga ttctgttgc  
110201 ctagttgtct acgaaggagt cctacactt ctgaacccca ctgcatttgg  
110251 gagtgcccta cagaatttgc atcaaagagt acaaataacct ggacagtggaa  
110301 ggagaaggac gtagctttag ggagctccac cttacagtgc ttgatattag  
110351 ctaaaacccca cgttctgttag taatttagcat gttcgttcca gaagtggcaa  
110401 tagatgttgc aatctgttcc acatacatgt ataaccatgc atgttttac  
110451 aagtctaaaca ttgtttctgc ttaaggagaa attaccatc ctgctgagca  
110501 atcctcagtg ctcatgttag ctgcctatgg aggtacatcc tcatcagtg  
110551 ttatggaa aaactggc acgcctgggtt caggagatgt ttagggttca  
110601 ccagggtggg atctgggtga gatgaagatg cagaatataat tccgatttgc  
110651 ggggtccctc aaggctgtg ctttgcattcc aggactgtat ggttaatttgc  
110701 ctctcttcac tacccttcat gttcccttct cctctcagcc agtgcacca  
110751 ttaggatgca tttagcagca ggtcacaaaaa gaagcagatt caactaccc  
110801 aaactataat gcaatttata ataccacata gaaagaggct cagagataag  
110851 acagctctcc acagagccctc agggctctgg cttcatttttct ctgatttct  
110901 gagttttttt ttgactttttt ccattctgtct gcctgcctcc tcctcaggct  
110951 ggaagcaaaa tggctacagc agttgcaata tcttctatag atgcaacact  
111001 ttccagaggca gaaagaggcc atctttagtgc tttatcttttctt cttaaaatgt  
111051 aggagaactg tccatttcaca tcttatttttgcagaatccctc atgcctaaaa  
111101 caatcaccag catggaggat gggaccgcca tcattggctg tcaccagtc  
111151 ggaccaggca gctggatctc ggccagactc ccctaaagca catgatcaag  
111201 tgggggggaa agtagctggc taaattttaag gatttagtt tgggatgtc  
111251 atttggggaa agcaacttcc catagtataa tatttgcata agccaagaaa  
111301 cctcttccac ttgggggtga gggtaaggag tcagcatgtc cttaaacatg  
111351 gtgttttctc tcaaatatttct tttatctatgc tcatttctgt tcctctaaat  
111401 gtccgggtt taaaacataaaagccaga tttataatttctt tttactttagt  
111451 tcttcattca catcattttcc atgaaacaaac aagcatagac tagactgtct  
111501 ctttgaattt caaatggaaag gcaaaatgggg taaaggaaca actagcaaaa  
111551 ataaataaaat tagtatttca atcatataat ctttcttcac atacagtcc  
111601 cccataaaatg ttcttatcacc accaccacta aggaaaaact ggtacaggcc  
111651 ctttcttc cacccttc gacacccctc gacacccctc tcttcagact  
111701 gtttcttgc gtgactcctt cttcatttgc aagttataaa ctaaccaggct  
111751 ctcaccaaa aatagcaaaa aagttagaaat acaccatgtg ggggtccaga  
111801 accctcaagt ctctttaaaag atagttcatc cccttctctt ctctctttaaa  
111851 ctcttaccta gtttcttaggc ccaccaggct accacaaaccc ttgtttgaaa  
111901 atatcaagat cactggaaaac agtgacaaaaa aggccaggatt ttaatgcata  
111951 ggttttgcaca actatccctga actaacagtc tcttgcattcc ataatggcc  
112001 attttcttcc aagcagtata aatcacagac tattcgtatt ttctatttgc  
112051 ctaattttatg cacacggact ttcattttac actaattccctc ttttatgtt  
112101 attttccaaat ggcattttcc tccctcatgt ttttctcagt cttccccagg  
112151 gacatttttg gtgtttccac aaaatggccaa gcaccacgct gcacatagca  
112201 tttttcttgc ctttccataa ttttgcatttgcact ttttgcatttgc ggccttgcatt  
112251 ataattttcc acatgtatgtc ttctggact ttctgaaatttgcataat  
112301 gactctgtat gtgtttgaca gaaataatttgcactt ttgtttaaaaggc  
112351 tagggcttcc acttaaccctg ttttgcatttgcactt ttctggactt gctgtataat  
112401 ctgagtaggg caccatcc ttttgcatttgcactt tatttgcatttgc gggatctgt  
112451 ggttttctt aatgtttaaga acaaaaaggat ttatttgcatttgcactt  
112501 taaaactttag aatatttatttgcactt ttcatatttgcactt ttttatgtt  
112551 gttggagtaa ttctatgcaaa aaccctacaa agggtattca gtaggattct  
112601 aaaacgcact ttctatgactt ctttgcatttgcactt ttgtttaaaa ccattacctg  
112651 aagaaatttgcactt ttctatgactt ttcatatttgcactt ttttatgtt  
112701 caggttctt attcagtccctc tcaggcatct tcattcaag acatatccct

## FIGURE 1AK

112751 ctcctctgct gtgtttcata tgtactcttg tccccctaag atctgcttct  
 112801 cctattgggt ggagagtgc ctctcaatct ctgttttcag accccaaatg  
 112851 actacgttat ttcttggatt tctgagaaga gttgtgtctt agtttgtttg  
 112901 gactgtata aaaaacatac cataaactag gcagcctata aacaacaat  
 112951 atttactct cacagtctg gaagctggaa gtc当地agarc atgggtgtgg  
 113001 aagattctgt gtc当地ggag ggcccacttc cactgtatg aaagggcag  
 113051 gttccttgc ggtctcttta tgagggcact aatcccattt attagggtctc  
 113101 tgccctcata gcctaaccat ctc当地cagagc cccacaccc taatactatc  
 113151 actttagggg ttagggattt aacataaaa ttctgggggg acacaaaacat  
 113201 tcagaccata acagggtgct tcttccatta cttttgtga aatgttgg  
 113251 cttagtttt agtgacgggg aatgtttt ctatttgtat aagactgaag  
 113301 ttccacactgg ctttctactc taatccaaat gcttttgc当地 ttatagaaca  
 113351 ggatttctgt cagatttctc taggttctgt cccatggtt gttgttactc  
 113401 tacagtgtata aggaaaatta tattctgttt ctgttgggtt ataaaatagc  
 113451 ttccctgttg agctctgaaat ggatttccatc tc当地cccttc cagcagaaaac  
 113501 tgagctgcca aatgacccctc gagtgctgccc ttaaccatac cttttggctt  
 113551 ctgttagatcc aggtttcatt gagaaaccca ggggtataaaa ctggagccct  
 113601 atatttgtt tcatcagcaa agtgtgtgtg catgtccaca ttgataactt  
 113651 aaaatgaatc tgaatgtgtt attagtatac tattgttaca tagcaaattt  
 113701 ccctcaattt agtgggttga aataaacat acttataatc tcacagttt  
 113751 tatggtcagg tatccagaag cagtttagct gaatgggtt ggtctaaaat  
 113801 ctcatatgag gttgcagtca agctcttggc tggagatgtt gggagaggac  
 113851 ccattaccaa gctcaactga gcatttgc当地 gcaggccctt tatttccctt  
 113901 ccacattatt cacacccctag gttgc当地aa tgccatatg acatgcagct  
 113951 ggcttcccc agagagagct gagagagatc gc当地agagaa gctgcagtc  
 114001 ttatgacat aagctcagaa gtttatgc当地 ategttctt tcatgtgtaa  
 114051 gtggtcaccaa agaccaaccc ttttacatgtt aggccaggac tatacagggg  
 114101 ggttaatccca ggagatggg gccacttggg accatgttag agtcaggcta  
 114151 ccacaaatgc cttcagatag attatgtttt ttaaatttgc当地 gatttcaacc  
 114201 agtccctatt gtttccag gaacccaaac caccaattcc ccattccctt  
 114251 cgacctctcc gtttacatc ttttacatc gacatgggtt tataacttct  
 114301 ggtcttaacca ttttatgtcc agtacatctt gtattatatac tcaaaaaaaaa  
 114351 aaaaaaaaaatcc tggcctcaac ctatagctac gcaattatatac tccactctt  
 114401 gtgcagactc tcaaaaaggaa tattaacaaa atattgagta ttttgc当地  
 114451 gcagcaacaa gtttacatc atgaggaggc caggtgc当地 gtttcatgcc  
 114501 ttttatccca gcaacttggg aggctgaggg ggttgc当地 cctgagggtca  
 114551 ggagttcgag accagccctgg tcaacatgtt gaaaccctgt ctctactaaa  
 114601 aataacaaaatcc ttagccaggc gtgggtggc当地 gc当地ctgtt当地  
 114651 tcaggaggct gaggcaggag aatcacttgc当地 atccaggaaag aggagggttgc  
 114701 agtgc当地tgc当地 ttttgc当地tgc当地 gc当地gggca当地  
 114751 actccatctc gaaaataaaaat aaataaaaat attgggggg caggacatgc  
 114801 actagtctg ttttgc当地tgc当地 aagtgttcaacttcaactc cagctctt  
 114851 ttttgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 114901 gtttgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 114951 caatatttag ttttgc当地tgc当地 ttttgc当地tgc当地  
 115001 aatttgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115051 aacagtccagg aatttctgttgc当地 agttaagga gatcaacca gaaaacttct  
 115101 aagaaatttt ttttgc当地tgc当地 ttttgc当地tgc当地  
 115151 atgcaaaatc ttttgc当地tgc当地 ttttgc当地tgc当地  
 115201 atactaagaa atagaagagg aaagcaagg ttttgc当地tgc当地  
 115251 gtggatgttgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115301 agtgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115351 acttttactg ttttgc当地tgc当地 ttttgc当地tgc当地  
 115401 ttttgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115451 ttttgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115501 ttttgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115551 caggaggagg gctgtacatc gagcttagcat ttttgc当地tgc当地  
 115601 taagttttac cacccttgc当地 cacccttgc当地 ttttgc当地tgc当地  
 115651 ggggaacaaa agcaccatcc ctttgc当地tgc当地 ttttgc当地tgc当地  
 115701 ataacccctgttgc当地 gtttgc当地tgc当地 ttttgc当地tgc当地  
 115751 ccattacaca aatcacaagaa ttttgc当地tgc当地 ttttgc当地tgc当地  
 115801 agtgc当地tgc当地 ttttgc当地tgc当地 ttttgc当地tgc当地  
 115851 tcacacttag ttttgc当地tgc当地 ttttgc当地tgc当地

FIGURE 1AL

115901 aaaattataat ttaatcgctt tcatggtgtg ctctacttgg taaagaagg  
 115951 gggaaacaag gttaagtaaa ggccaggatc cttttctgc aatggatgac  
 116001 tgacatggga aagagatgag ttacccaggc tttgtttttt gctacctgca  
 116051 gtataaaaact ccctgacatt gtcggaaattt gcttttacag gtatTTatt  
 116101 ttcaacatct aatTTgtcg gcttttcttc ctttgcattc tttttcttct  
 116151 ttggccatgt ataatgcata acaacaattt ctgaactcca aaagcataga  
 116201 aacccatgaa taacattacc tgggaaaaat taatctctct acctccagct  
 116251 accaagagaa tcatttgcac atgaaacccct gagatttgcg tctttcatta  
 116301 atctaattgc gtagcaattt ttataccaca tcgttctatt ggaatttgatg  
 116351 actaatttattt cccaaaactt ttttggaaactt atttgcatttca taatTTTtg  
 116401 ttttggatttga aaaaatgtcat gacccttatattt ctcttcatgt tatctgttgc  
 116451 atagctaacc ctctccctca gatttagtgg cttaaaacag caaccatttg  
 116501 tttagcccac aatttgcattt ggcagtttctt ctggctttaa gtgaactgac  
 116551 tcatgcttgc tggcatttttgc ttgttgcatttgc tggactaagg  
 116601 tggcttcgtt tagaattact gctttttgc catgtggctt ctcatttc  
 116651 agcaggctgg gctgggttac atgggtgggg tgggttccca agagcagttac  
 116701 attgatatactt gaaaggcttca tgaagtttgc gtcatttttttca  
 116751 atgtccacta tggcatttttttgc gtcatttttttca atggcaaggg  
 116801 gcaagagaca gagaaggaga ttccacccctt tcatgttgc gatctgcattt  
 116851 gtcgtggcca gtatttgcattt ctaccatccc agccatttttca  
 116901 ctttttttttttgc ttttttttttgc tatgttgcatttca  
 116951 ctaatttgcattt ttttttttttgc ttttttttttgc atccatttttca  
 117001 aagaaagaaa agggaaaatag catttttttttgc accttcatgttca  
 117051 ggcttagacat ttttttttttgc ttttttttttgc taatacacac  
 117101 tgcagatzaag gaaatttgcatttca ttttttttttgc ttttttttttgc  
 117151 atttcatttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117201 ttcaaaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc  
 117251 catataatttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117301 ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117351 gtcatttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117401 atacccatgttcat ttttttttttgc ttttttttttgc ttttttttttgc  
 117451 aaacaaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc  
 117501 gggtaacat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117551 gttggaaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc  
 117601 ctgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117651 ttgacttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117701 agaaaacttac ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117751 acgtggtagc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117801 agggggaaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117851 acctcccccatttca ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117901 gatTTgggttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 117951 ctccagcatttca ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118001 ggttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118051 tggtttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118101 cccctcttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118151 gtacttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118201 gtcacacccatttca ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118251 ttgagcccat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118301 ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118351 cccagccatttca ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118401 gttggaggttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118451 acagaacaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118501 atttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118551 ctatcttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118601 atgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118651 ataaaggccatttca ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118701 acttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118751 ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118801 ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118851 agggaaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118901 agttaaaatgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 118951 gatgttcat ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc  
 119001 ctcttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc ttttttttttgc

FIGURE 1AM

119051 taataaagata taatgtgtgt aaaattcttg tacaatcccc agcacagaat  
 119101 aggtgctcaa tatattaaat atattgttat tatttattaa ttaattaatg  
 119151 ctgatttctg cattaatttt gactaattga aatctggac ttgcttaatt  
 119201 tgcgtgtatt tgcgttccct tcttccagta cttgatggca atttctacct  
 119251 gtggtaaatg gaacgttaaa agttatatgc ttatacaacac tttagtcctt  
 119301 tattcccttgg agtgagttt aagagtcctc atgttgaata attcatgtaa  
 119351 tcacagaaat aatactatgt atcagggacc gcttccttta taaaagataa  
 119401 aggcagtggaa aatactgcct ttgtcagaaa tacttcagtt actctgagag  
 119451 agagagacat ttgttacta tatgacagca cagtcgtatgg caaataatag  
 119501 aagtttggaa aatatttatt ttgaatgaat gaataatgaa cacattgtga  
 119551 acaaataaaat ggttactat ttaatttattc aggaatcaat taagctttat  
 119601 taataaaaaat tggggggggg tttttaaaag cccacacaca aatgagaggc  
 119651 atcacagagg caaacggat gacattatta aaatcggtat tgctgaatca  
 119701 cagttcagca ataagcaagt gtttgggca ttcaaaaataag tgagtatttg  
 119751 agtgactcta agaagataat gaaactccctc cactttttt cagttgcaat  
 119801 aatttttaag gaacatataa aaacatattt tagtggccctt atttgaataa  
 119851 agatagtata tataacatata gcaattaaaaa agaagaaaga aaacaaattt  
 119901 taatgtgttt ttctttcac cttatgggca gttactagat gtatnnnnnn  
 119951 nnnnnagcttc atctggcccg tagaaaaacag ttcagaaaaag tattcatatt  
 120001 taaaactggg gaggctgttag aaaaagaaga aagaataata ttggcaagac  
 120051 aattggctga ccttatacat atcttgggtt atcagcttac tctgtgagta  
 120101 tccccccctt tccacgttag aaaaatttcg caacatgttt caaatttgcgg  
 120151 atgggtgtt tatttaactg gcaattttt cttgcagCTG ACACAGCCCC  
 120201 TGGCACTGAT GATGTATATG ATGAAAAAAGG ATGCCAGTGT GATGTATACAG  
 120251 TGGAAAGACCT CACCCCCACCA CTTAAAAACTG TCATTCGAGC TATCAGgttg  
 120301 gtgaaaatct tgaacaacgt gattcagaga cataactttag attaattgaa  
 120351 ttactatgtt gctaaggttt ttttctgcag gtaaatatcc tggaaaaacc  
 120401 actttccctt tccttattcat nnnnnnnnnn aataagagtgt tttgcaaaaca  
 120451 catttgcata tcaaaaatgc atgttagttcc ataaaagacc attttacac  
 120501 cctttatatt ttttaaggga tgcttattact agatgttgc tcttggactt  
 120551 ctggagatttgc catggaaaag tttagattgc attttgactt taacttacat  
 120601 tcagggtttc aacggacatt aaaaaggca aacacttagt gttcagccctc  
 120651 ttttttagtg tggttttcta ttcttaaggt gttgtctcac atgagatgtt  
 120701 cttaaatgtt ccactgtata ctcaggctt tatattacac atctgcagaa  
 120751 gccaaaaata atttgcata tgactttcc ccccagagtt tcttattata  
 120801 tttaactgtt aactttttt gtaacttata ttaacagagt tataaaagatt  
 120851 aataatgtt atgttccat acagAATTAT GAAATTTCAT GTTGCAAAAC  
 120901 GGAAGTTTAA GGAAACATTA CGTCATATG ATGTAAGAAGA TGTCAATTGAA  
 120951 CAATATTCG CTGGTCATCT GGACATGTTG TGTAGAATTAA AAAGCCTTC  
 121001 AACACGGtaa gcaatggaaa tgcatttttct tggtaaaggaa tgggcata  
 121051 acctatcttag gaagaacttc tcttttagtag agtaaacctc tgaactccat  
 121101 atttttcattt catttttagt gggcaatgg aatttgcattt aaacattgat  
 121151 ttatatttgc ttttaacata gatataactc aggcatccaa agcatccaa  
 121201 tgcgttcatatt tccttgcattt taaaaatggg aagaaaagttt gttcttgctt  
 121251 tataagggttgc tcatgaggat tgaacaagttt aatgcattgtt attcataaca  
 121301 tgtaacaggc ctgttactgt gtcttataaa catcaatggg tgggtgtgat  
 121351 gtttgaattt ttactgtgtc tgatcctaaa ttatctaaat tccattttatt  
 121401 atctaaatttca taatcatcct ttgggaataaa cgtactattt ctccttcatt  
 121451 aagtttccatc caaccatcca acctgtgaag acgggcctt ctctgacett  
 121501 tatacagtag cagagtctac tgcagagcac aagagcactc agaatctcgg  
 121551 tgcgttggc caaaggtagg acttggccct tgcgttgcattt cctgggtgca  
 121601 agtgcgttca ccttgcgttgc gactaagact gaggtccttc attcatgtcc  
 121651 tgcgttggc tacaatata ctatcccttctt agtagcatct tattgagtg  
 121701 tttaaaagaaa tgaattccat atgtttaattt caaccacata tgggtgattt  
 121751 tgattatctc aaagccaaaaa tattcgtttt attcgtttt ttaagagcc  
 121801 tgcttttattt ccacccaaaa ttaccacat ttgtgattgt atagtgc  
 121851 aaatgcaggactt gactttttt tttttttttt tttttttttt tttttttttt  
 121901 gcccaggatgtt aggcatatfaa tggggcccttta gtaaaaatacc tgggttcat  
 121951 ttgttataaga aataacaatt tggtaatca ttttagcaggat aattatttgg  
 122001 cccatcatgt gtggcaggac ctgtggacat ccagagattt gaaaaataat  
 122051 gacccaggacc ttgttagatgtt tgcgtttttt tttttttttt tttttttttt  
 122101 ngaacatctg aacatgacca gagattgtgg tcatatttgc atctctgcct  
 122151 agatggccat ggccttctaa gtttttaat aaaactgtct acagctccca

Exon 11

Exon 12

### Exon 13

### Exon 14

125351 TATGAAAACA TATTGCCTGA TGGCAGAAC TAACTTTATAA GTGGTCAACT  
125401 TCTACACAAG CGTATGAAAT ACTGGTCAGT AGAACAGCCA TTGTGATTGG  
125451 ACTGGTTTCT CTGCAATGGC GCCAACCCCCA GGCTTGCCAA TACTGCTAT  
125501 GTAAAGGGCA AGTGTGAGAA GCTATTCTCA TTTCGCTGAC ATACAGGTAG  
125551 GACTATGGGG GATGGGACAT TTGAGTGGGA CTGAGATAGG AAAGGCTTGA  
125601 AAAGAACCCA GAAACACCAC CAGGAAGTTG GCAGAAGTAAA AGAAAATGAC  
125651 TTCCCCCTCA AAGGGCAATG AGAGGGAGAG AAACAAACCA AAATAGAAGA  
125701 ACTAGACTT TTAGAAAATG AGTATTGCTA GGGATTCAA CTACCTAATC  
125751 TTCCCTTATT CTTATATATA AGCAGAGAAT TTTTGCAAGG TATTTATTTT  
125801 TTAATATGCC CTGAATGCT TTTGCTATTA TGTGTACATT TTGCATATGA  
125851 AAGTCTAAAA CGAAAGTTTC TTTACTTTT ATACTGTAGT GAAAATTTTC  
125901 TATTCTTCCC AAGAATGTTG TCCCAAATCT GAAATTACTG GTTCAATTTC  
125951 CTGATATAAA

FIGURE 2A

## KCN6q cDNA

1	CTGGAGTGAGGCGCGGGAAAGATGCCTGGTCTTGCCTCGCGACTGGCA	50
51	GCCGCGTCTGCGGGCTGTCCACTGAACGTGAGGACTGCGGCCGGTGG	100
101	CCTGAGGGAGAGCCGCCGGGCAAGCAGGGGGCCGGATGAGCCTGCTGG	150
1	M S L L G	5
151	GGAAGCCGCTCTTACACGAGTAGCCAGAGCTGCCGCGCAACGTCAAG	200
6	K P L S Y T S S Q S C R R N V K	21
201	TACCGGGGGTGCAGAACTACCTGTACAACGTGCTGGAGAGACCCCGCG	250
22	Y R R V Q N Y L Y N V L E R P R G	38
251	CTGGGCGTTCATCTACCACGCTTCGTTTCTCCTGTCTTGTTGCT	300
39	W A F I Y H A F V F L L V F G C L	55
301	TGATTTGTCAGTGTCTTCTACCATCCCTGAGCACACAAAATTGGCCTCA	350
56	I L S V F S T I P E H T K L A S	71
351	AGTTGCCCTTGTATCCTGGAGTCGTGATGATTGTCGTCCTGGTTGGA	400
72	S C L L I L E F V M I V V F G L E	88
401	GTTCATCATTGAACTCTGGCTGCGGGTTGCTGTTGTCGATATAGAGGAT	450
89	F I I R I W S A G C C C R Y R G W	105
451	GGCAAGGAAGACTGAGGTTGCTCGAAAGCCCTCTGTGTTATAGATACC	500
106	Q G R L R F A R K P F C V I D T	121
501	ATTGTTCTTATCGCTTCAATAGCAGTTGTTCTGCAAAAACTCAGGGTAA	550
122	I V L I A S I A V V S A K T Q G N	138
551	TATTTTGCCACGTCTGCACTCAGAAGTCCTCCCTACAGATCCCTCC	600
139	I F A T S A L R S L R F L Q I L R	155
601	GCATGGTGCATGGACCGAAGGGGAGGCACCTGGAAATTACTGGGTTCA	650
156	M V R M D R R G G T W K L L G S	171
651	GTGGTTATGCTCACAGCAAGGAATTAATCACAGCTGGTACATAGGATT	700
172	V V Y A H S K E L I T A W Y I G F	188
701	TTTGGTTCTTATTTTCTGTCTTCCTTGTCTATCTGGTGGAAAAGGATG	750
189	L V L I F S S F L V Y L V E K D A	205
751	CCAATAAAGAGTTTCTACATATGCAGATGCTCTGGTGGGGCACAATT	800

FIGURE 2B

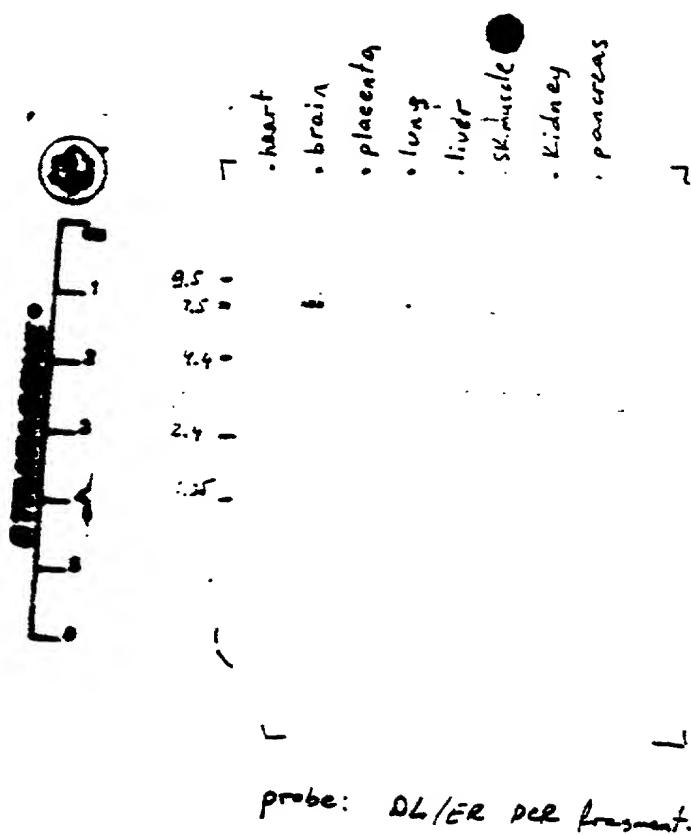
206	N K E F S T Y A D A L W W G T I	221
801	ACATTGACAAC TATTGGCTATGGAGACAAA ACTCCCCTAAC TTGGCTGGG	850
222	T L T T I G Y G D K T P L T W L G	238
851	AAGATTGCTTCTGCAGGCTTGCACTCCTGGCATTCTTCTTGAC	900
239	R L L S A G F A L L G I S F F A L	255
901	TTCCCTGCCGGCATTCTGGCTCAGGTTTGCAATTAAAAGTACAAGAACAA	950
256	P A G I L G S G F A L K V Q E Q	271
951	CACCGCCAGAAACACTTGAGAAAAGAAGGAACCCAGCTGCCAACCTCAT	1000
272	H R Q K H F E K R R N P A A N L I	288
1001	TCAGTGTGTTGGCTAGTTACGCAGCTGATGAGAAATCTGTTCCATTG	1050
289	Q C V W R S Y A A D E K S V S I A	305
1051	CAACCTGGAAGGCCACACTTGAAAGGCCCTGACACCTGCAGCCCTACCAAG	1100
306	T W K P H L K A L H T C S P T K	321
1101	AAAGAACAAAGGGAAAGCATCAAGCAGTCAGAAGCTAAGTTAAGGAGCG	1150
322	K E Q G E A S S S Q K L S F K E R	338
1151	AGTGCACATGGCTAGCCCCAGGGGCCAGAGTATTAGAGGCCAACGCCT	1200
339	V R M A S P R G Q S I K S R Q A S	355
1201	CAGTAGGTGACAGGAGGTCCCCAACGCACCGACATCACAGCCGAGGGCAGT	1250
356	V G D R R S P S T D I T A E G S	371
1251	CCCACCAAAGTGCAGAAGAGCTGGAGCTTCACGACCGAACCCGCTCCG	1300
372	P T K V Q K S W S F N D R T R F R	388
1301	GCCCTCGCTGCGCCTCAAAAGTTCTCAGCCAAAACCAGTGTAGATGCTG	1350
389	P S L R L K S S Q P K P V I D A D	405
1351	ACACAGCCCTGGCACTGATGATGTATGATGAAAGGATGCCAGTGT	1400
406	T A L G T D D V Y D E K G C Q C	421
1401	GATGTATCAGTGGAAAGACCTCACCCACCACTAAA ACTGTCAATTGAGC	1450
422	D V S V E D L T P P L K T V I R A	438
1451	TATCAGAATTATGAAATTTCATGTTGCAAAACGGAAAGTTAAGGAAACAT	1500
439	I R I M K F H V A K R K F K E T L	455
1501	TACGTCCATATGATGTAAGATGTCATTGAACAATATTCTGCTGGTCAT	1550
456	R P Y D V K D V I E Q Y S A G H	471

1551	CTGGACATGTTGTAGAATTAAAGCCTCAACACGTGTTGATCAAAT	1600
472	L D M L C R I K S L Q T R V D Q I	488
1601	TCTTGGAAAAGGGCAAATCACATCAGATAAGAAGAGCCGAGAGAAAATAA	1650
489	L G K G Q I T S D K K S R E K I T	505
1651	CAGCAGAACATGAGACCACAGACGATCTCAGTATGCTCGGTGGGTGGTC	1700
506	A E H E T T D D L S M L G R V V	521
1701	AAGGTTGAAAAACAGGTACAGTCCATAGAATCCAAGCTGGACTGCCTACT	1750
522	K V E K Q V Q S I E S K L D C L L	538
1751	AGACATCTATCAACAGGTCTTCGGAAAGGCTCTGCCTCAGCCCTCGCTT	1800
539	D I Y Q Q V L R K G S A S A L A L	555
1801	TGGCTTCATTCCAGATCCCACCTTTGAATGTGAACAGACATCTGACTAT	1850
556	A S F Q I P P F E C E Q T S D Y	571
1851	CAAAGCCCTGTGGATAGCAAAGATCTTCGGGTTCCGCACAAAACAGTGG	1900
572	Q S P V D S K D L S G S A Q N S G	588
1901	CTGCTTATCCAGATCAACTAGTGCCAACATCTCGAGAGGCCCTGCAGTTCA	1950
589	C L S R S T S A N I S R G L Q F I	605
1951	TTCTGACGCCAAATGAGTTAGTGCCAGACTTCTACCGCCTAGCCCT	2000
606	L T P N E F S A Q T F Y A L S P	621
2001	ACTATGCACAGTCAGCAACACAGGTGCCAATTAGTCAGCGATGGCTC	2050
622	T M H S Q A T Q V P I S Q S D G S	638
2051	AGCAGTGGCAGCCACCAACACCATTGCAAACCAAATAAACGGCACCCA	2100
639	A V A A T N T I A N Q I N T A P K	655
2101	AGCCAGCAGCCCCAACAACTTTACAGATCCCACCTCCTCTCCAGCCATC	2150
656	P A A P T T L Q I P P P L P A I	671
2151	AAGCATCTGCCAGGCCAGAAACTCTGCACCCCTAACCTGCAGGCTTACA	2200
672	K H L P R P E T L H P N P A G L Q	688
2201	GGAAAGCATTCTGACGTCACCAACCTGCCTTGTGCCTCCAAGGAAAATG	2250
689	E S I S D V T T C L V A S K E N V	705
2251	TTCAGGTTGCACAGTCAAATCTCACCAAGGACCCTATGAGGAAAAGC	2300
706	Q V A Q S N L T K D R S M R K S	721
2301	TTTGACATGGGAGGAGAAACTCTGTTGTCTGTCCCAGGTGCCGAA	2350

722	F D M G G E T L L S V C P M V P K	738
2351	GGACTTGGGCAAATCTTGTCTGTGAAACCTGATCAGGTGACCCGAGG	2400
739	D L G K S L S V Q N L I R S T E E	755
2401	AACTGAATATAACAACCTTCAGGGAGTGAGTCAGTCAGGCAGC	2450
756	L N I Q L S G S E S S A S R G S	771
2451	CAAGATTTACCCCAAATGGAGGGAAATCCAACCTGTTATAACTGATGA	2500
772	Q D F Y P K W R E S K L F I T D E	788
2501	AGAGGTGGGTCCCAGAGACAGAGACAGACACTTTGATGCCGCACCGC	2550
789	E V G P E E T E T D T F D A A P Q	805
2551	AGCCTGCCAGGGAAAGCTGCCTTGATCAGACTCTCTAAGGACTGGAAGG	2600
806	P A R E A A F A S D S L R T G R	821
2601	TCACGATCATCTCAGAGCATTTGTAAGGCAGGAGAAAGTACAGATGCCCT	2650
822	S R S S Q S I C K A G E S T D A L	838
2651	CAGCTTGCCTCATGTCAAACGTAAAGTTCTCATTTCTTCCAGGC	2700
839	S L P H V K L K	846
2701	ATAGCAGTTCTTAGCCATACATATCATTGCATGAACATTTGAAAGCC	2750
2751	CTTCTAAAAAGTTGAAATTGCAAGAACATGGGAAGAACATGAAAGGCAGTT	2800
2801	TATAAGCCGTTACCTTTAATTGCATGAAAATGCATGTTAGGGATGGC	2850
2851	TAAAATTCCAAGGTGCATCGACATTAACCCACTCATTAGTAATGTACCT	2900
2901	TGAGTTAAAAGCCTGAGAACCAACACAGCTAATGCTATGGGTGTAT	2950
2951	GAATATGTCAAGTTAGGTCAATTAGAAGATTGACACTGTATTGAAA	3000
3001	TTATGGGAGTAAACACCTTCAAATTTCAGGCATTCTGCTTGTGACTAA	3050
3051	ATACAAACTACATTTCAGGATTAGGCCATAATGTATATTAAACACAAT	3100
3101	GGCTATCAACAGCTGCTAATAAGGTATCAACTAAAGCAGAATTGGGAAT	3150
3151	AATAGAAAATGGCTGCTTATTCAAGATATATTGCCAACCCATTCTATT	3200
3201	CAGTCATTATTATTAAATGTAATTGAAATGTCAATTGTGTGCTTTGG	3250

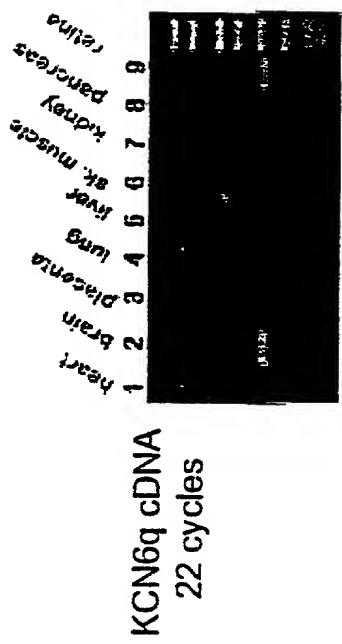
3251	TGATTTAGCGCTGTGGCAAGCAATTTGCACATCATTTCATGTTGTTCT	3300
3301	TTATGACAAGAATGTTCTTCAATTAGAAAATGTGCAAATAATGAAATTCA	3350
3351	GGGCCAGTGAGGCAAATAGACTATCTGACATATTGACTTTATGAAAACA	3400
3401	TATTGCCTGATGGCAGAATCAACTTATAAGTGGTCAACTTCTACACAAG	3450
3451	CGTATGAAATACTGGTCAGTAGAACAGCCATTGTGATTGGACTGGTTCT	3500
3501	CTGCAATGGCGCCAACCCCAGGCTTGCCTAACTGCCTATGTAAAGGGCA	3550
3551	AGTGTGAGAAGCTATTCTCATTTCGCTGACATACAGGTAGGACTATGGGG	3600
3601	GATGGGACATTTGAGTGGGACTGAGATAGGAAAGGCTTGAAAAGAACCCA	3650
3651	GAAACACCACCAAGGAAGTGGCAAAGTAAAAGAAAATGACTTCCCCCTCA	3700
3701	AAGGGCAATGAGAGGGAG	

## FIGURE 3A



## FIGURE 3B

## RT-PCR analysis of the KCN6q gene expression in human tissues



## FIGURE 4A

KCN6q\_ .....MS.....LLGKPLS.....  
 KCNQ4\_ MAEAPPRLGIGPPPGDAPRAELVALTAQSEQGEAGGGGSPRRLGLLGSPPLPGAPLPG  
 consensus masapprrrigigpppgdaprraelvaltaqseqgeaggg sprrigllg pl pgapipg  
  
 KCN6q\_ YTS.SQS.CR.RN...VK.YRRVQNY1YNVLERPRGWAFYHAFYFLLVFGCLLSVEST  
 KCNQ4\_ PGSGCSACGQRSSAAKRYRRVQNY1YNVLERPRGWAFYHVFYFLLVFSCLLSVILST  
 consensus Sgs Sac qr saa Kryrrvqny1ynvlerprgwafyh FyFLLVF CLILSV ST  
  
 KCN6q\_ IPEHTKLIASSCLLILEEVMIVVFGLEIIRIWSAGCCCRYRGWQGRFRFARKPFCVIDTI  
 KCNQ4\_ IPEHTKLIASSCLLILEEVMIVVFGLEIIRIWSAGCCCRYRGWQGRFRFARKPFCVIDTI  
 consensus I EH LA CLLILEEVMIVVFGLEIIRIWSAGCCCRYRGWQGR RFARKPFCVID I  
  
 KCN6q\_ VLEASIAVVAKTOGNIFATSALRSIRFLQILRMVRMDRRGGTWKLGSVVYAHSKELIT  
 KCNQ4\_ VLEASIAVVAAGTQGNIFATSALRSIRFLQILRMVRMDRRGGTWKLGSVVYAHSKELIT  
 consensus V IASIAVV A TQGNIFATSALRSIRFLQILRMVRMDRRGGTWKLGSVVYAHSKELIT  
  
 KCN6q\_ AWYIGFLVLIF SFLVYLVEKDANKFSYADALWWGTITLTTIGYGDKTPHTWLGRILS  
 KCNQ4\_ AWYIGFLVLIF A SFLVYLAEKDANSFSYADSLWWGTITLTTIGYGDKTPHTWLGRILS  
 consensus AWYIGFLVLIF SFLVYL EKDAN & Fstc YAD LWWGTITLTTIGYGDKTP TWLGRILS  
  
 KCN6q\_ AGFALLGISFFALPAGILGSGFALKVQEQRQKHFEKRRPAANLIQCVWRSYAADEKS.  
 KCNQ4\_ AGFALLGISFFALPAGILGSGFALKVQEQRQKHFEKRRPAANLIQAAWRLYSTD.MSR  
 consensus AGFALLGISFFALPAGILGSGFALKVQEQRQKHFEKRR PAANLIQ WR Y De Sr  
  
 KCN6q\_ .VSIATWK...H1K.....ALH.....  
 KCNQ4\_ AYLTAIWYDSDILPSFRELALLFEHVQRARNGLRPLEVRRAPVDPGAPSRYPPVATC  
 consensus a ATW yds L sfralAL fehvqrarnggirplieavrrrapvpdgapsryppvatic  
  
 KCN6q\_ .P..TKKEQGEASSSQQKLSPKDRMRMSP.R..GOSIKSRQASVGDRRSPSTHITIPE...  
 KCNQ4\_ RFGSTSFCFGE..SSRMG.IKDRMRMGSQRRRTGPS.KQQLAPPTMPTSPSSQVGEATS  
 consensus rPgst GEasss s KevRMRas qrrtg SIK A SPstd aEgts  
  
 KCN6q\_ PTKVQKSWSFNDRTFRPSLRLKSSQPSPVIDAATALG...D...V...EKGQOC...V...D...T...P  
 KCNQ4\_ PTKVQKSWSFNDRTFRASLRK...P...TSA...DAP...E...V...A...E...K...S...Y...O...C...V...D...T...P  
 consensus PTKVQKSWSFNDRTFRPSLRLKssqpKpv Ad A gtddv dkk QCdvsVeDl P  
  
 KCN6q\_ .KTVIRAIIRIMKFVAKRKFKETLRLPYDVKDVIQEYSAAGHLDMLCRIKSLQTRVDQIIGK  
 KCNQ4\_ .KTVIRSIIRIMKFVAKRKFKETLRLPYDVKDVIQEYSAAGHLDMLCRIKSLQTRVDQIIGK  
 consensus IKTIVIR IRIMKF VAKRKFKETLRLPYDVKDVIQEYSAAGHLDML RIKSLQTRVDQIIGK  
  
 KCN6q\_ GQITSDDKSRK...ITAHETTD...SM...GRVVKVKEQVQSI...SKLD...CLLD...IVQQVLRKG  
 KCNQ4\_ G...PGD...KAREKGDKGPSBAEVVD...SM...GRVVKVKEQVQSI...E...K...L...L...L...G...F...V...S...R...C...L...R...S...G  
 consensus Gqi DKK REKgdk e E Dd1SM1GRVVKVKEQVQSI...KLD...LL...Y...LR...G  
  
 KCN6q\_ .SASALALISFO...PPFEC...QTS...TSDY...Q...SPV...D...SKD...SG...SAQ...NS...G...C...S...R...S...T...S...A...N...I...S...R...G...L...Q...F...I...L  
 KCNQ4\_ TSAS...L...G...A...V...Q...M...P...L...F...D...P...I...T...SDY...H...S...P...V...D...H...D...S...V...S...A...Q...T...L...S...I...S...R...S...V...S...T...N...I...D...  
 consensus tSASalalA Qip Fe e TSDY SPVD D1S SAQT SgclSRS S N1 rglqfil  
  
 KCN6q\_ TPNEFS...AQT...FY...A...L...S...P...T...M...H...S...Q...A...T...Q...V...P...I...S...Q...S...D...G...S...A...V...A...A...T...N...T...I...A...N...Q...I...N...T...A...P...K...P...A...P...T...T...L...O...I...P...P  
 KCNQ4\_ .....  
 consensus tpnefs...aqt...fy...a...l...s...p...t...m...h...s...q...a...t...q...v...p...i...s...q...d...g...s...a...v...a...a...t...n...t...i...a...n...q...i...n...t...a...p...k...p...a...p...t...t...i...q...i...p...p  
  
 KCN6q\_ PLPAIKHLPRPETLHPNPGLOESISDVTTCLVASKENVQVAQSNLTDRSMRKSFDMMG  
 KCNQ4\_ .....  
 consensus pipaikhlprpetlhpnpgloesisdvttclvaskenvqvaqsnltkdrsmrksfdmmg  
  
 KCN6q\_ ETLLSVC...PMV...PKDLG...K...S...L...V...Q...N...L...I...R...S...T...E...E...L...N...I...Q...L...G...S...E...S...S...A...R...G...S...Q...D...F...Y...P...K...W...R...E...S...K...L...F...I...T  
 KCNQ4\_ .....  
 consensus etllsvc...pmv...pkdlg...ks...l...sv...q...n...l...i...r...s...t...e...e...l...n...i...q...l...g...s...e...s...s...a...r...g...s...q...d...f...y...p...k...w...r...e...s...k...l...f...i...t  
  
 KCN6q\_ DEEVGPEETETDTFDAAPQPAREAAFA...S...L...R...T...G...R...S...R...S...Q...S...I...C...K...A...G...E...S...T...D...A...L...S...L...P...H...V...K...L...K  
 KCNQ4\_ .....  
 consensus deevgpeetetdtfdapqparesafasdsrltgrsrsqsicksagestdalsiphvklik

FIGURE 4B

## FIGURE 4C

KCN6q\_ LIRIMFELVAKRKFKETLRLPYDVKDVIQEYQYAGHLDMLCRIKSLQTRVDQIVGAGQ.ITSQ  
 KCNQ4\_ LIRIMFELVAKRKFKETLRLPYDVKDVIQEYQYAGHLDMLCRIKSLQTRVDQIVGAG...PGD  
 KCNQ2\_ VCKMFLVSKRKFKETLRLPYDVKDVIQEYQYAGHLDMLCRIKSLQTRVDQIVGAGPAITDK  
 KCNQ3\_ VRIKOPRKKPKETLRLPYDVKDVIQEYQYAGHLDMLCRIKSLQTRVDQIVGAGPAITDK  
 KCNQ1\_ LRRMOPFVAKKEQQARIPYDVRDVIEQYQYAGHLDMLCRIKSLQTRVDQIVGAGPS...LP  
 consensus trimkflvaKrkfkat1rPYDVkDVIEQYQYAGHLDMLsRIKsLQtrDqivgkpp it  
  
 KCN6q\_ SKSREK. .... ITAEHETTD .... DLSMGRVKVEKQVQSSESKLDCLP  
 KCNQ4\_ SKAREKGDK. .... GFSCEAEVVD .... DLSMGRVKVEKQVQSSEHKLDCLP  
 KCNQ2\_ D..RTKG. .... PAEAEIP.... EDPSMMGRVKVEKQVLSNEKKLDFLW  
 KCNQ3\_ BKKSQKGSAFTFESQOSPRNEPVVAR. PSTSEIEDQSMMGIPVKVEQVQDNCCKLDFLW  
 KCNQ1\_ ISVSEK. .... SKDR.GSN.... DSGARLNRVEDKVTOXZORLAET  
 consensus kk reKg ftfpsqqsprn p eaevp seiedismmgtrvvkvekqVqsiekLd 11  
  
 KCN6q\_ DMYQQQLRKG. SASAALALSFQEPPEFCEQTSQVPSQPVDSK.... DLSGSAQ.NSGC.SRS  
 KCNQ4\_ GFYSRCRLRSQTSAS... LQAVQMPLEDPPEITSQVPSQVDSK.... DLSVSAQTLS.SRS  
 KCNQ2\_ NEMYMRKG... IPPTETEIV.. FGKEPEPAPPYHSPEDSMEHEDRHEGCIV.... KIVRS  
 KCNQ3\_ DASHMOHHEH.. LQVQTEYVPTKGTSQPAEAK... KKEDNKE. YSDLK.... TICN  
 KCNQ1\_ DFLHOMESLHGGSTPGCCEPREGCAHITQPCGGGSVDPPELQPSNTLPTYEQLTQPRR  
 consensus diymqvirkg sas lt aypqigafapeq sdyhspvDsk yvdlagsaq s tisrs  
  
 KCN6q\_ SANISGLOFILTPNEFSAOTFYALSPTMHSQATQVPSQSDGSAVAATNTIAQINTA  
 KCNQ4\_ VSTNMD....  
 KCNQ2\_ SGSTCGK... NFSAPPAA.... PPVQCPPT.... SWQ.... PQSHPR.GHGTS  
 KCNQ3\_ YSETG.... PPE.... PPYSFHQVTEIDKVSQYCGFFAHPDVNLPR.G.GPS  
 KCNQ1\_ GPDEGS....  
 consensus ts garginq ppe saqtifyalpp q t is a p n prng gts  
  
 KCN6q\_ HKPRAPTLQIIPPELPAIKRGPPEIHPNPAGLQESISDVTTCLVASKENHQVAQSNLT  
 KCNQ4\_ BV.GDHEGSLVRIPPPAH... ER. SLSAYGEGN.... RASMEPI. ROEDTP  
 KCNQ2\_ .... SGKXOATPPSSATTYMERPTVLPILTLLDS.... RVSCHS.... QADLQ  
 KCNQ3\_ ....  
 KCNQ1\_ ....  
 consensus p pa gtlq pp pa lerp tl ag esisdvttelras e vqv q dl  
  
 KCN6q\_ KDRSMRKSFDMGGETLLSVCVPMVPKDLGKSL.SVSNLIRSTEELNIQLSGSESSASRGSQ  
 KCNQ4\_ ....  
 KCNQ2\_ G...CRPPECTLR.... D. SDTSXSKPSVD.... HEELERSPSGFSISQSNL  
 KCNQ3\_ GPYSDRISPRQRSSITR.... D. SDTPISLMSVN.... HEELERSPSGFSISQDR...  
 KCNQ1\_ ....  
 consensus g s r s r tlrsvcpdvpdsd is1 svqnliirsheelers sgfsisqsr  
  
 KCN6q\_ DYPKWRKRESKLEETDEEVGPEETETDTFDAAPQE.... AREAMPASDSICRTGRSIS  
 KCNQ4\_ DAENSCYAVAPCAKVRPYAEGESEDTSDLCTPCGPPRSATGEGPFGDVGVAGPRK...  
 KCNQ2\_ DDFGPNGGSSNNR2KR.YAEGEGETDTDADPFTPSGSMPBLSSSTGOG. ISDSWATPSNKPI  
 KCNQ3\_ ....  
 KCNQ1\_ ....  
 consensus dfl aa fi d r yiaegatdtasd tp g p satgeg sdslwtg k  
  
 KCN6q\_ QSICKAGESTDALSLPHVKLK  
 KCNQ4\_ ....  
 KCNQ2\_ ....  
 KCNQ3\_ ....  
 KCNQ1\_ ....  
 consensus qsickagestdalslphvklik

**DECLARATION AND  
POWER OF ATTORNEY  
FOR UTILITY OR DESIGN  
PATENT APPLICATION  
(37 CFR 1.63)**

Declaration Submitted with Initial Filing       Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

OR

Attorney Docket Number	20430P
First Named Inventor	Petrushkin, et al.
<b>COMPLETE IF KNOWN</b>	
Application Number	09/937,499
Filing Date	September 26, 2001
Group Art Unit	
Examiner Name	

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*(Title of the Invention)*

the specification of which

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Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Attorney Docket Number	Priority Claimed? YES      NO
PCT/US00/09587	PCT	04/10/2000	20430-PCT	<input checked="" type="checkbox"/> <input type="checkbox"/>
				<input type="checkbox"/> <input type="checkbox"/>
				<input type="checkbox"/> <input type="checkbox"/>
				<input type="checkbox"/> <input type="checkbox"/>

Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	Attorney Docket Number
60/129,274	04/14/1999	20430PV

## DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

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Customer Number  → Place Customer Number Bar Code Label here  
 OR  
 Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Joseph A. Coppola	38,413	Jack L. Tribble	32,633

Direct all correspondence to:  Customer Number or Bar Code Label

**000210**

Name	Joseph A. Coppola				
Address	Merck & Co., Inc. - Patent Department				
Address	P.O. Box 2000, RY60-30				
City	Rahway	State	NJ	ZIP	07065-0907
Country	USA	Telephone	(732)594-6734		Fax (732)594-4720

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:	<input type="checkbox"/> A petition has been filed for this unsigned inventor				
Given Name (first and middle [if any])			Family Name or Surname		
KONSTANTIN			PETRUKHIN		
Inventor's Signature	<i>Konstantin Petrukhin</i>			Date	December 6, 2001
Residence: City	Collegeville	PA	Country	US	Citizenship RU
Post Office Address	Merck & Co., Inc., P.O. Box 2000				
City	Rahway	State	NJ	ZIP	07065-0907

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Supplemental Sheet

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C. THOMAS		CASKEY					
Inventor's Signature					Date		
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WEN		LI					
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MICHAEL L.		METZKER					
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PATENT APPLICATION  
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Declaration Submitted with Initial Filing **OR**  Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e))

<b>Attorney Docket Number</b>		20430P
<b>First Named Inventor</b>		Petrushkin, et al.
<b>COMPLETE IF KNOWN</b>		
<b>Application Number</b>		09/937,499
<b>Filing Date</b>		September 26, 2001
<b>Group Art Unit</b>		
<b>Examiner Name</b>		

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*(Title of the Invention,*

the specification of which

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PCT/US00/09587	PCT	04/10/2000	20430-PCT	<input checked="" type="checkbox"/>	<input type="checkbox"/>
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Application Number(s)	Filing Date (MM/DD/YYYY)	Attorney Docket Number
60/129,274	04/14/1999	20430PV

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Address	Merck & Co., Inc. - Patent Department				
Address	P.O. Box 2000, RY60-30				
City	Rahway		State	NJ	ZIP
Country	USA	Telephone	(732)594-6734	Fax	(732)594-4720

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KONSTANTIN	PETRUKHIN				
Inventor's Signature				Date	
Residence: City	Collegeville	State	PA	Country	US
Post Office Address	Merck & Co., Inc., P.O. Box 2000				
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C. THOMAS 		CASKEY					
Inventor's Signature				Date	12/6/01		
Residence: City	Lansdale 	State	PA	Country	US	Citizenship	US
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
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WEN		LI					
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Inventor's Signature				Date			
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FEB 07 2002

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WEN	WEN	LI	L					
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Application Number(s)	Filing Date (MM/DD/YYYY)	Attorney Docket Number
60/129,274	04/14/1999	20430PV

## DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information known to me to be material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Application Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/US00/09587	04/10/2000	
60/129,274	04/14/1999	

Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint, respectively and individually, as my attorneys or agents with full power of substitution and revocation, the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Customer Number  Place Customer Number Bar Code Label here  
 OR  
 Registered practitioner(s) name/registration number listed below

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**000210**

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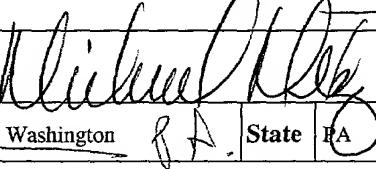
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:	<input type="checkbox"/> A petition has been filed for this unsigned inventor				
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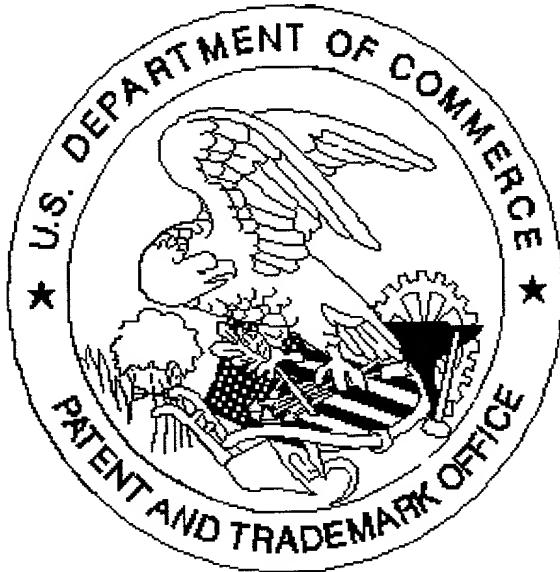
Additional inventors are being named on the 1 supplemental Additional Inventors(s) sheet(s) PTO/SB/02A attached hereto.

## DECLARATION AND POWER OF ATTORNEY

ADDITIONAL INVENTOR(S)  
Supplemental Sheet

Name of Additional Joint Inventor, if any:		<input type="checkbox"/> A petition has been filed for this unsigned inventor					
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Residence: City		State		Country		Citizenship	
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City	Rahway	State	NJ	ZIP	07065-0907		

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*Scanned copy is best available. Some Figures are dark.*